Resistant Hypertension: Definitions, Current Treatment and Emerging Approaches

Debbie Cohen, MD
Professor of Medicine
Director of Hypertension Programs
University of Pennsylvania
Philadelphia, PA

Penn Medicine

Disclosures

- Research and advisory board funding – Medtronic and Recor
- Consultant – Novartis

Resistant Hypertension

BP that remains elevated above patient's individualized target despite the concurrent use of 3 antihypertensive agents of different classes, ideally including diuretic, administered at maximum or maximally-tolerated doses and at the appropriate dosing frequency

OR

BP that is controlled to patient's individualized target with ≥4 antihypertensive medications, ideally including diuretic, administered at maximum or maximally-tolerated doses and at the appropriate dosing frequency

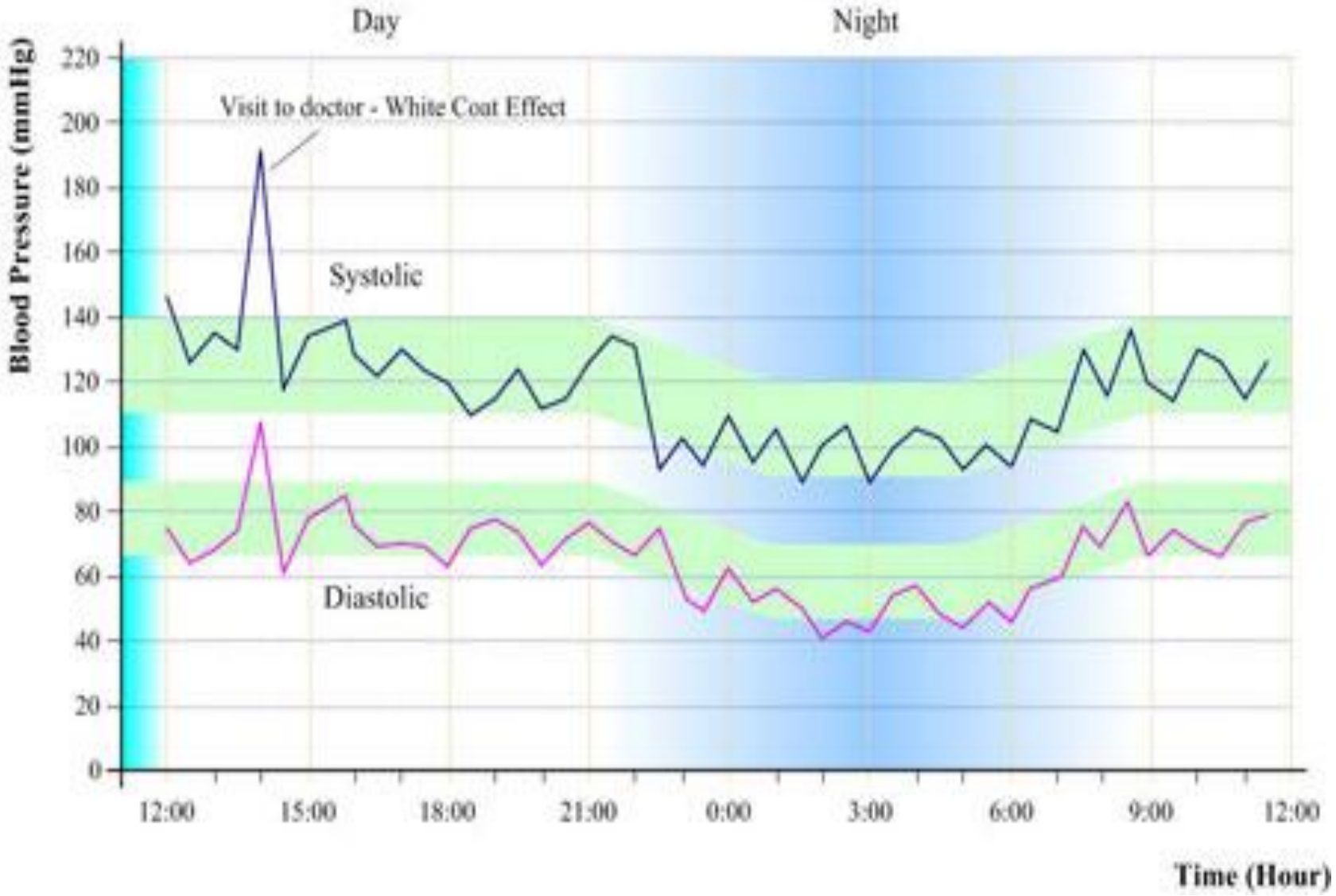
AHA Scientific Statement: **Resistant Hypertension: Diagnosis, Evaluation, and Treatment;** 2018

Resistant Hypertension

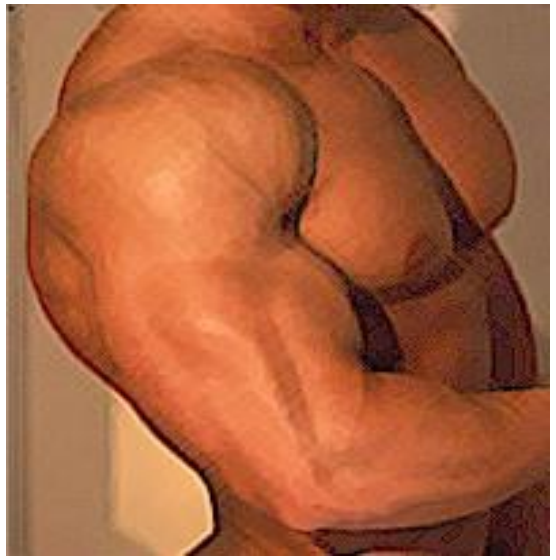
Need to first establish true resistant HTN and not apparent RH:

- Ensure **proper technique** in BP measurement
- Exclude "**white coat hypertension**" by performing out-of-office BP measurements.
- Exclude antihypertensive medication **nonadherence**

White Coat Hypertension



Big Arm + Small Cuff = High BP

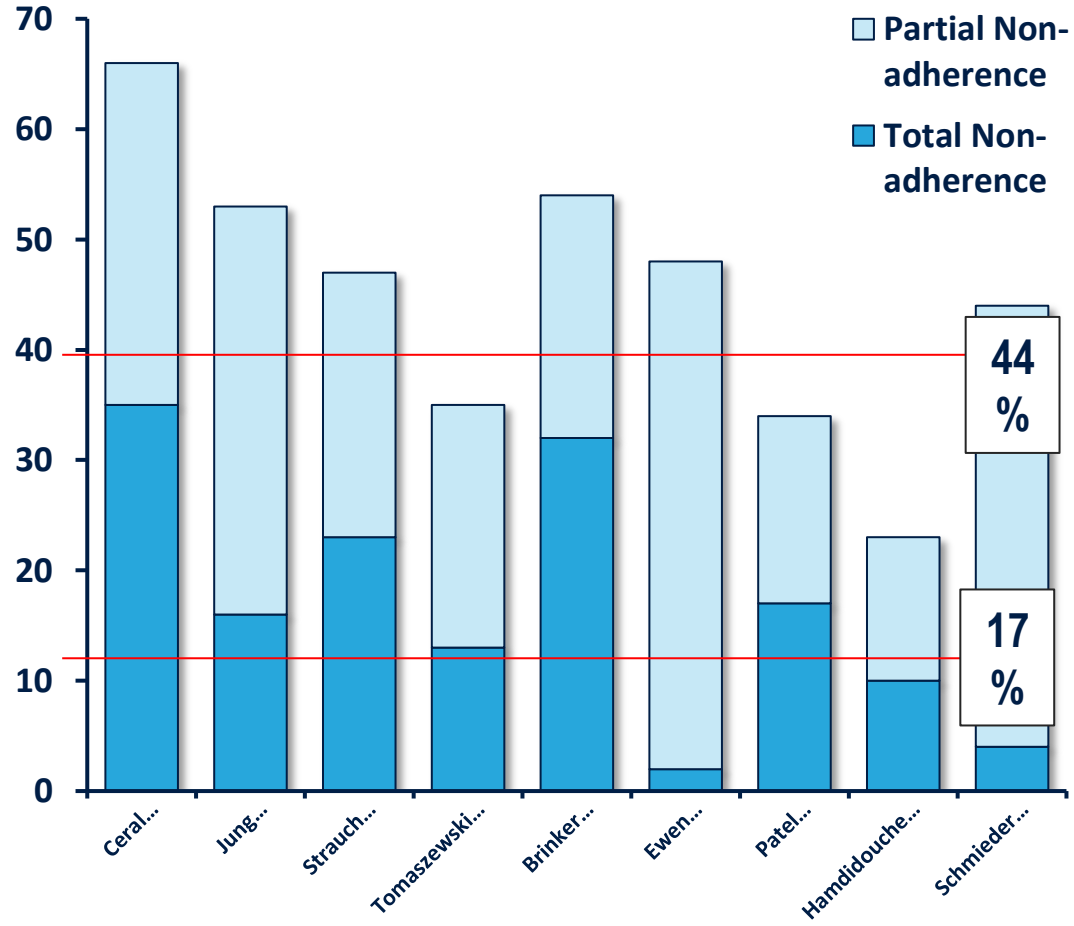


Effect of Improper Technique on BP

		Protocol 1		Protocol 2		
Author	**Population**	**Method**	**BP**	**Method**	**BP**	**Notes**
Mourad	Normotensive	Arm dependent	113/72	Arm horizontal	103/62	Similar results observed for ambulatory blood pressure monitoring
	Hypertensive	Arm dependent	163/88	Arm horizontal	145/79	
Webster	Hypertensive	Arm dependent	158/104	Arm horizontal	140/90	
Adiyaman	Hypertensive	Legs crossed	147/88	Legs uncrossed	140/86	
	Diabetics	Legs crossed	138/76	Legs uncrossed	130/74	
Fonseca-Reyes	Large arm circumference	Standard cuff	125/80	Large cuff	118/74	Prevalence of large arm circumference >40% in family medicine and hypertension clinics

Non-Adherence to Prescribed Antihypertensive Drugs in Clinical Studies

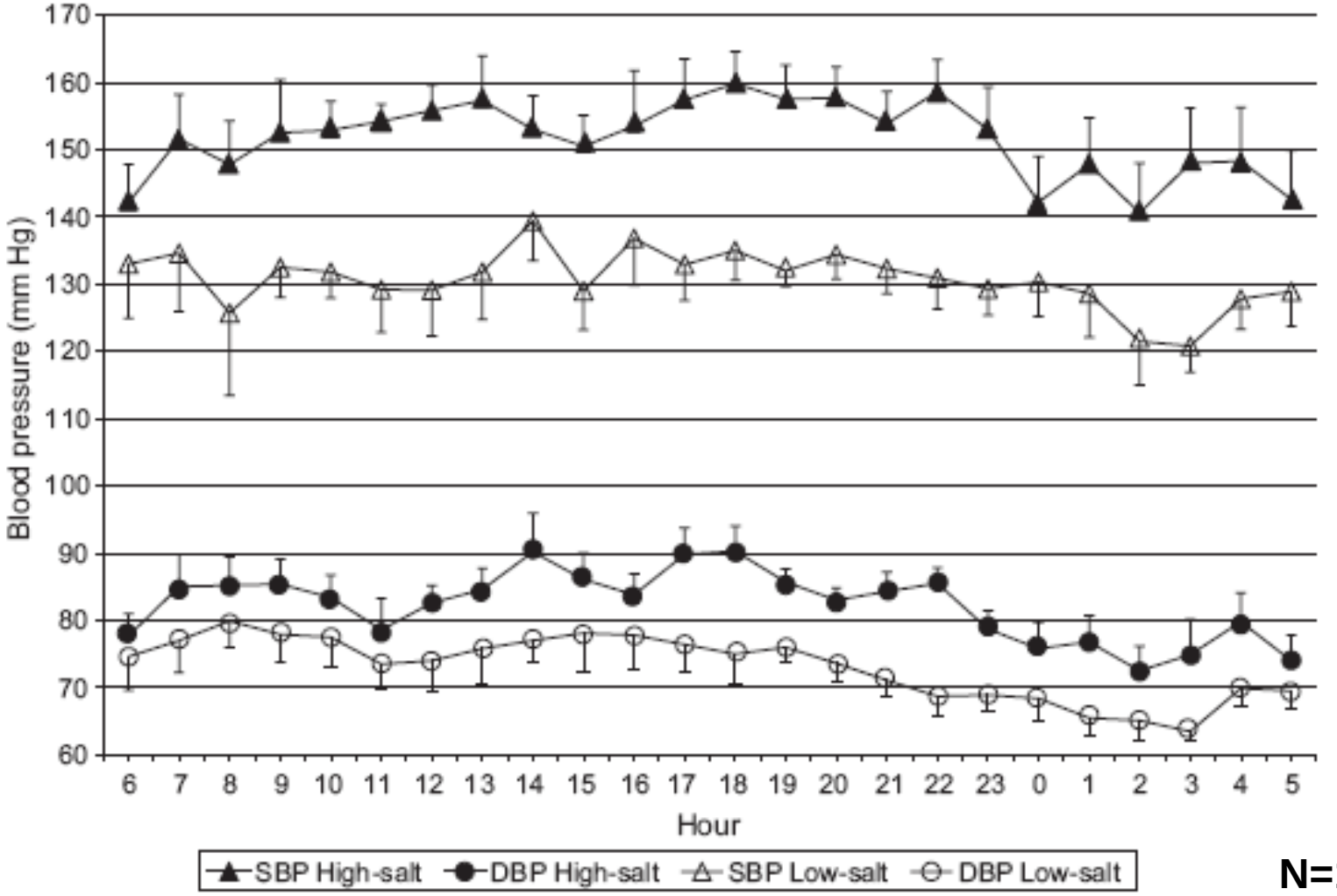
- 30 to 50% non-adherence rate is consistent between clinical trials and medical practice
- Poor and dynamic adherence introduces variability to trial endpoints
  - Not easily controlled, even with rigorous trial design



Clinician empathy increases patient trust, motivation, and adherence to therapy

Berra E, et al. Hypertension. 2016;68:297-306

Sodium Intake



N=12

Low- compared to high-salt diet decreased office SBP and DBP by 22.7 and 9.1 mm Hg, respectively

Pimenta Hypertension 2009;54:475-481

Interfering Substances

Medications That Can Interfere with Blood Pressure Control
Nonnarcotic analgesics
Nonsteroidal anti-inflammatory agents, including aspirin
Selective COX-2 inhibitors
Sympathomimetic agents (decongestants, diet pills, cocaine)
Stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, amphetamine, methamphetamine, modafinil)
Alcohol
Oral contraceptives
Cyclosporine
Erythropoietin
Natural licorice
Herbal compounds (ephedra or ma huang)

Whelton PK et al. Hypertension. 2018;71: e13-e115

Initial Evaluation

- ABPM
- Plasma Renin Activity and Aldosterone
- Plasma metanephrines
- CT angiogram/MRA
- Sleep study

- Need to individualize approach depending on symptoms and clinical suspicions

Management of Resistant Hypertension

Step 1

Exclude other causes of hypertension, including secondary causes, white-coat effect and medication nonadherence

+

Ensure low sodium diet (<2400 mg/day)
Maximize lifestyle interventions
- ≥ 6 hrs uninterrupted sleep
- Overall dietary pattern
-Weight loss
-Exercise

+

Optimize 3-drug regimen
Ensure adherence to 3 of different classes (RAS blocker, CCB, diuretic) at maximum or maximally tolerated doses. Diuretic type must be appropriate for kidney function*

BP not at target

Step 2

Substitute optimally dosed thiazide-like diuretic: i.e. chlorthalidone or indapamide* for the prior diuretic

BP not at target

Step 3

Add mineralocorticoid receptor antagonist (MRA): spironolactone or eplerenone**

BP still not at target

Note: Steps 4-6 are suggestions on the basis of expert opinion only and these steps should be individualized.

Step 4

Check Heart Rate: Unless <70 beats/ min, **add beta blocker** (eg. metoprolol succinate, bisoprolol) or combined alpha-beta blocker (eg. labetalol, carvedilol). If beta blocker contradicted, consider central alpha-agonist i.e. clonidine patch weekly or guanfacine at bedtime). If these are not tolerated, consider once daily diltiazem.

BP still not at target

Step 5

Add hydralazine* ** 25mg three times daily and titrate upward to max dose; in patients with congestive heart failure with reduced ejection fraction, hydralazine should be administered on a background isosorbide mononitrate 30 mg daily (max. dose 90 mg daily)

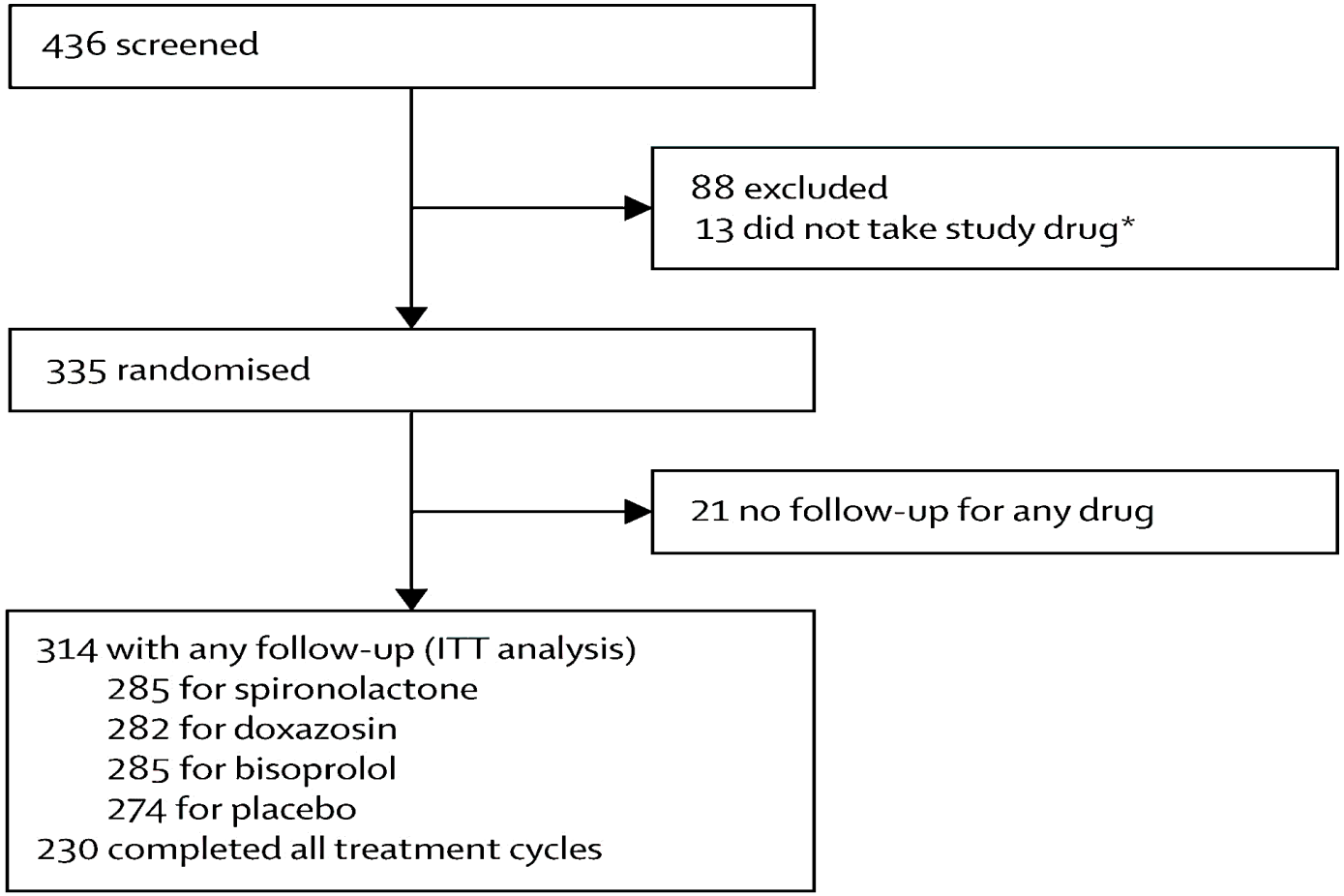
BP still not at target

Step 6

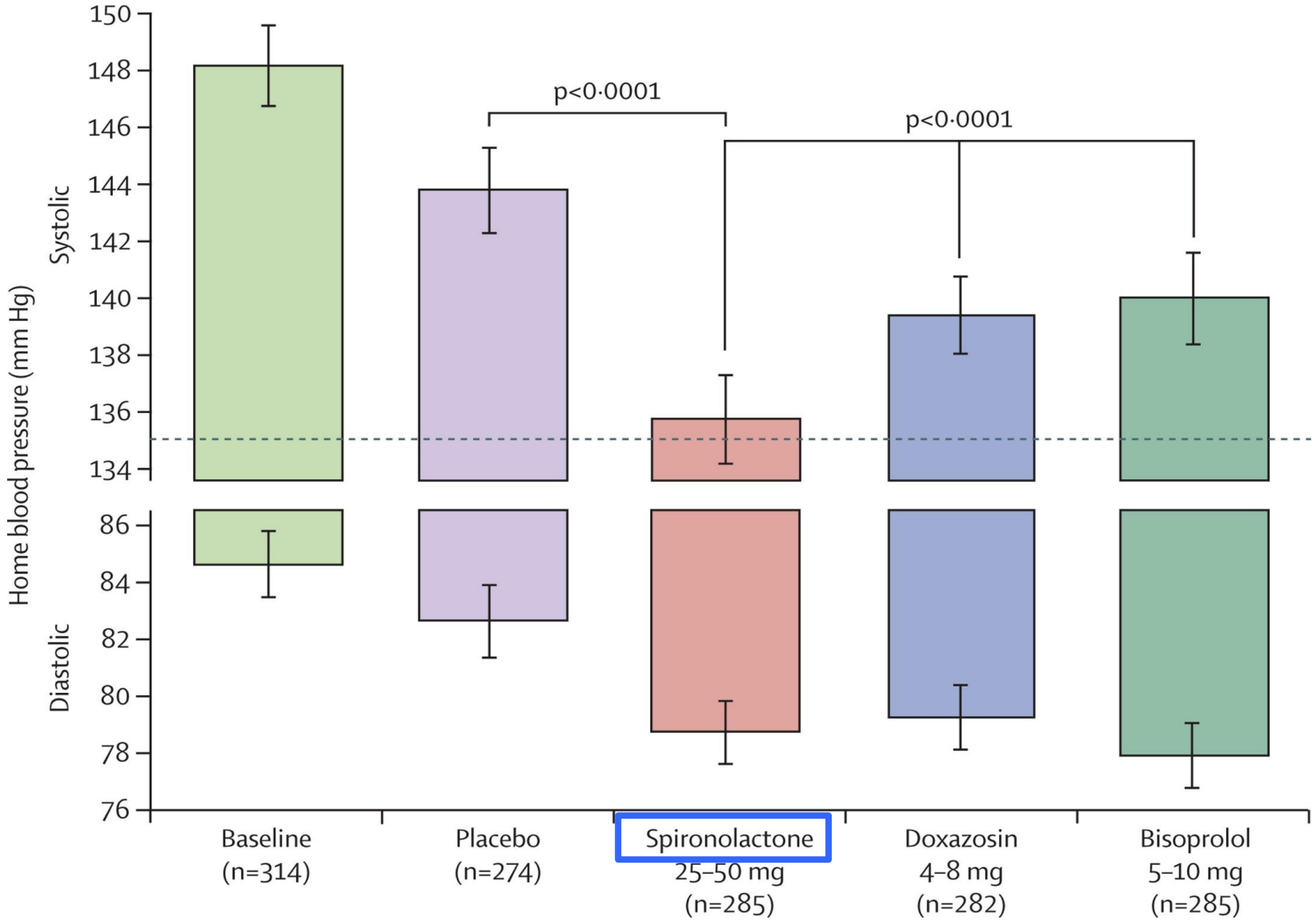
Substitute minoxidil** ** 2.5mg two to three times daily for hydralazine and titrate upward. If BP still not at target, consider referral to a hypertension specialist and/or for ongoing experimental studies- www.clinicaltrials.gov

Carey RM, et.al. Hypertension 2018;72:e53-e90.

PATHWAY-2 Study: Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension: a randomised, double-blind, crossover trial

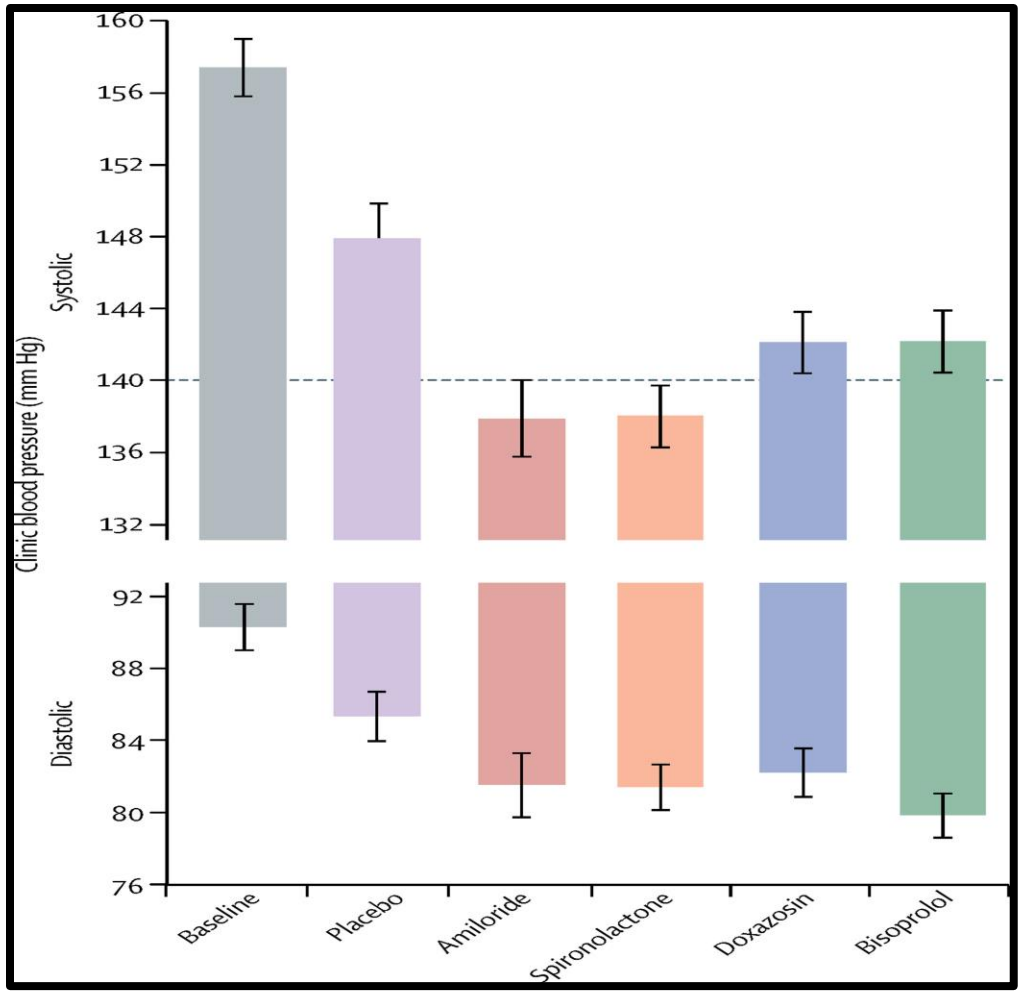


Williams B, et.al. Lancet 2Williams B, et.al. Lancet 2015;386 (10008):2059-2068.



Williams B, et.al. Lancet 2015;386 (10008):2059-2068

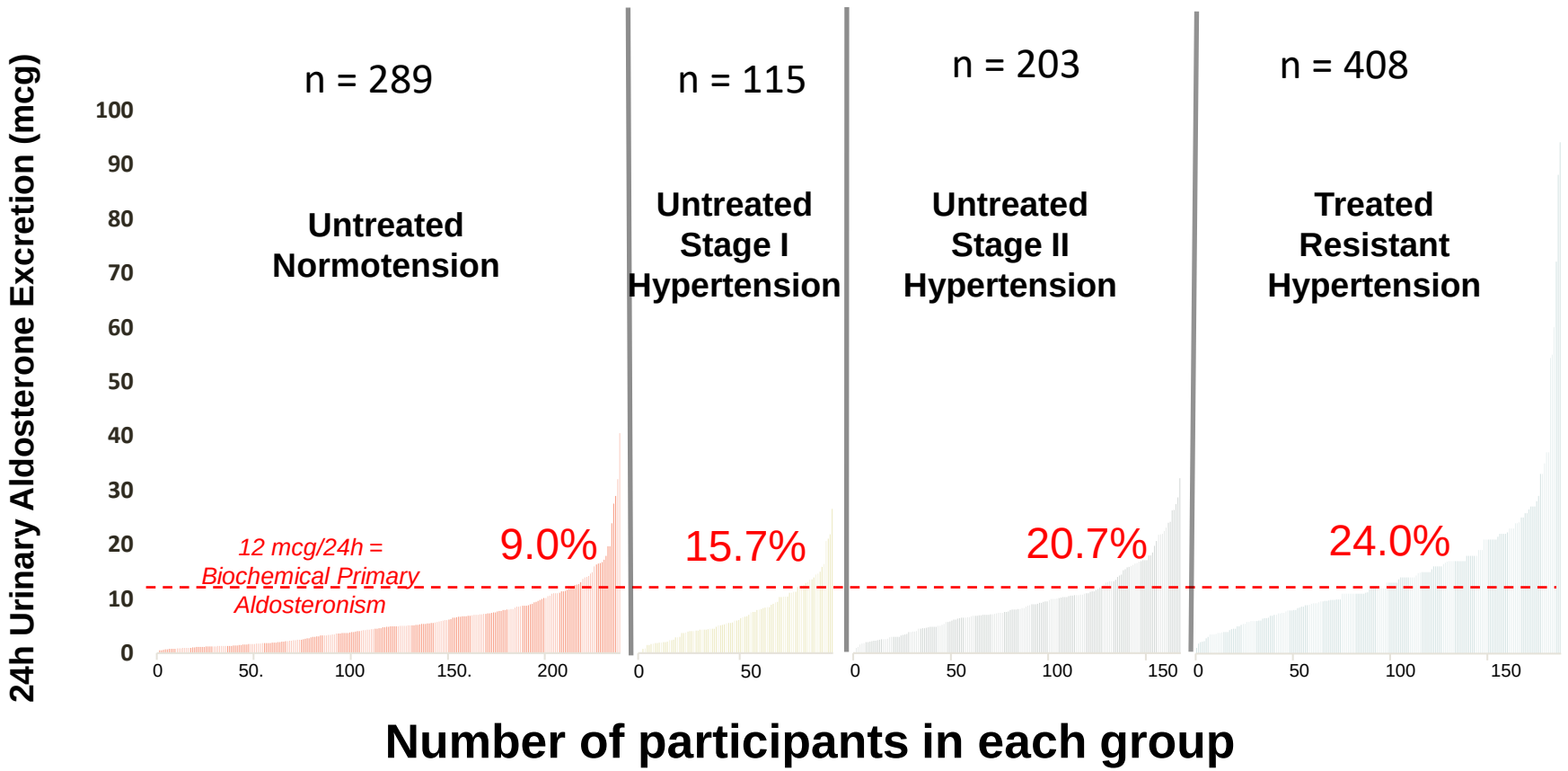
Effect of placebo, amiloride, spironolactone, doxazosin, and bisoprolol on clinic BP after 6 weeks of treatment



Both amiloride and spironolactone reduced SBP and DBP (unadjusted means) versus placebo (p<0·0001) and versus both doxazosin or bisoprolol (p<0·0001).

The Lancet Diabetes & Endocrinology 2018 6464-475DOI: (10.1016/S2213-8587(18)30071-8)

Prevalence of Primary Aldosteronism



Brown JM, Siddiqui M, Calhoun DA, Carey RM, Hopkins PN, Williams GH, Vaidya A. The Unrecognized Prevalence of Primary Aldosteronism: A Cross-sectional Study. Ann Intern Med. 2020 Jul 7;173(1):10-20.

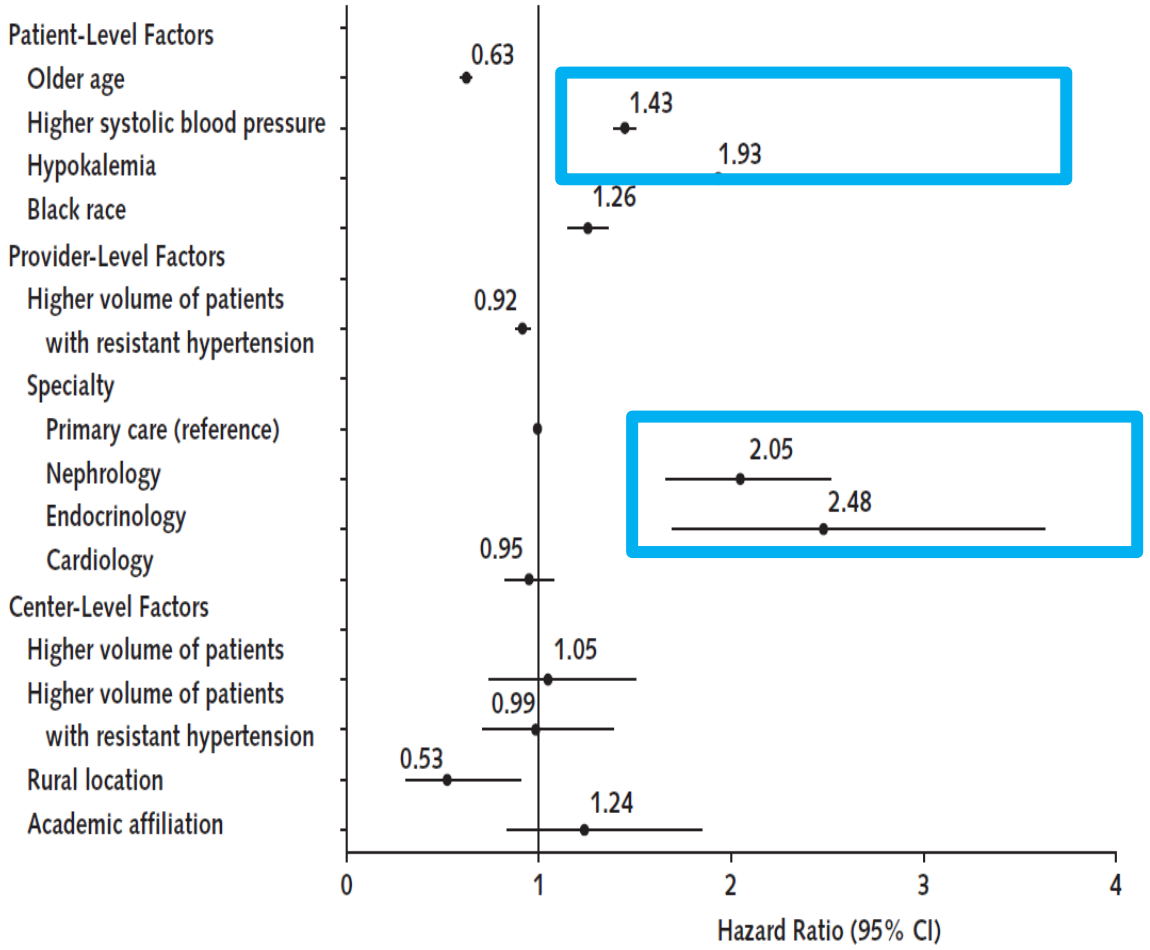
Testing for Primary Aldosteronism and MRA Use Among U.S. Veterans : A Retrospective Cohort Study.

	Overall cohort	No testing	Testing
	N=269,010	N=264,733	N=4,277
Key Baseline Patient-Level Factors			
Age, years	65 (58, 72)	65 (58, 72)	59 (52, 66)
Female sex, n (%)	11,009 (4%)	10,675 (4%)	334 (8%)
Black Non-Hispanic, n (%)	50,883 (19%)	49,517 (19%)	1,366 (32%)
Systolic blood pressure, mmHg	140 (132, 150)	140 (132, 150)	145 (136, 156)
Hypokalemia, n (%)			
	8,313 (3%)	7,878 (3%)	435 (10%)
ASCVD, n (%)	64,479 (24%)	63,677 (24%)	802 (19%)
Antihypertensive class, n (%)			
ACEI or ARB	218,059 (81%)	214,571 (81%)	3,488 (82%)
dCCB	105,656 (39%)	103,562 (39%)	2,094 (49%)
Thiazide or thiazide-like diuretic	159,219 (59%)	156,306 (59%)	2,913 (68%)
Beta-blocker	173,369 (64%)	170,779 (65%)	2,590 (61%)
Other	176,815 (66%)	174,380 (66%)	2,435 (57%)
Number of antihypertensive classes, n (%)			
Three	218,523 (81%)	215,215 (81%)	3,308 (77%)
Four	48,337 (18%)	47,450 (18%)	887 (21%)
Five or more	2,372 (1%)	2,290 (1%)	82 (2%)
Adherence, %	89 (68, 98)	89 (68, 98)	88 (63, 99)

Cohen JB, et al. *Ann Intern Med*. 2020. doi: 10.7326/M20-4873

Fewer than 2% of Veterans with incident treatment-resistant hypertension underwent guideline-recommended testing for primary aldosteronism

Appendix Figure. Association of patient-, provider-, and center-level factors with testing for primary aldosteronism.



Higher likelihood of appropriate initiation of MRAs for management of treatment-resistant hypertension (even in the absence of biochemical evidence of primary aldosteronism)

Cohen JB, et al. *Ann Intern Med*. 2020. doi: 10.7326/M20-4873

Pheochromocytoma

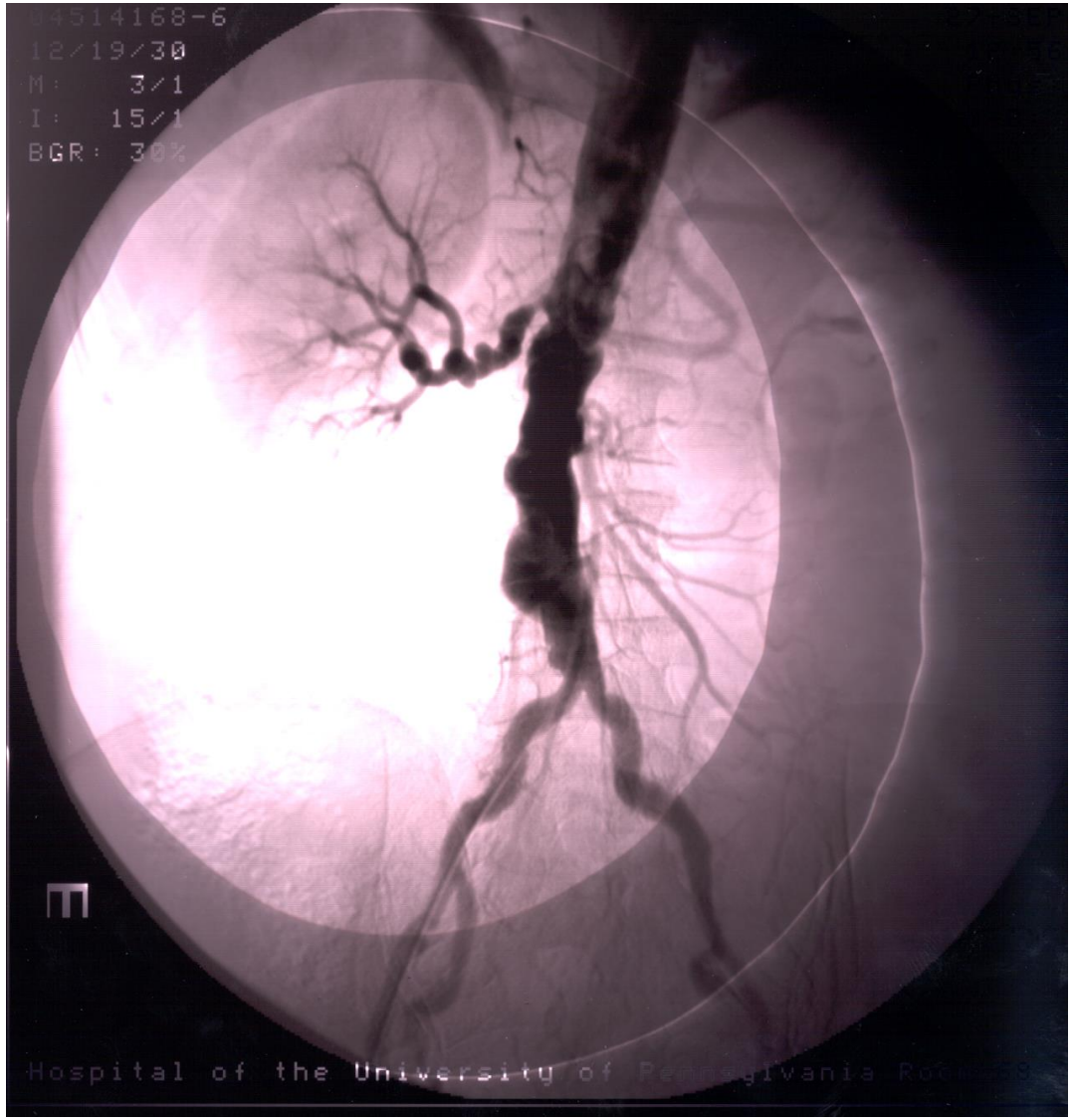
PCC/PGL Screening Tests

	Hereditary	Sporadic
	sensitivity/specificity (%)	sensitivity/specificity (%)
Plasma Met ★	**97/96**	**99/82**
Plasma Cat	69/89	92/72
Urine Met ★	**96/82**	**97/45**
Urine Cat	79/96	91/75
Total Urine Met	60/97	88/89
VMA	46/99	77/86

Adapted from Lenders et al. JAMA 2002

Atherosclerotic Renal Artery Stenosis (ARAS): Clinical Characteristics

- Older, men > women
- Generalized atherosclerosis
- Smokers
- Correlates:
  - HTN
  - Chronic kidney disease (ischemic nephropathy)
  - Frequently diabetic
  - Volume overload
    - “Flash” pulmonary edema

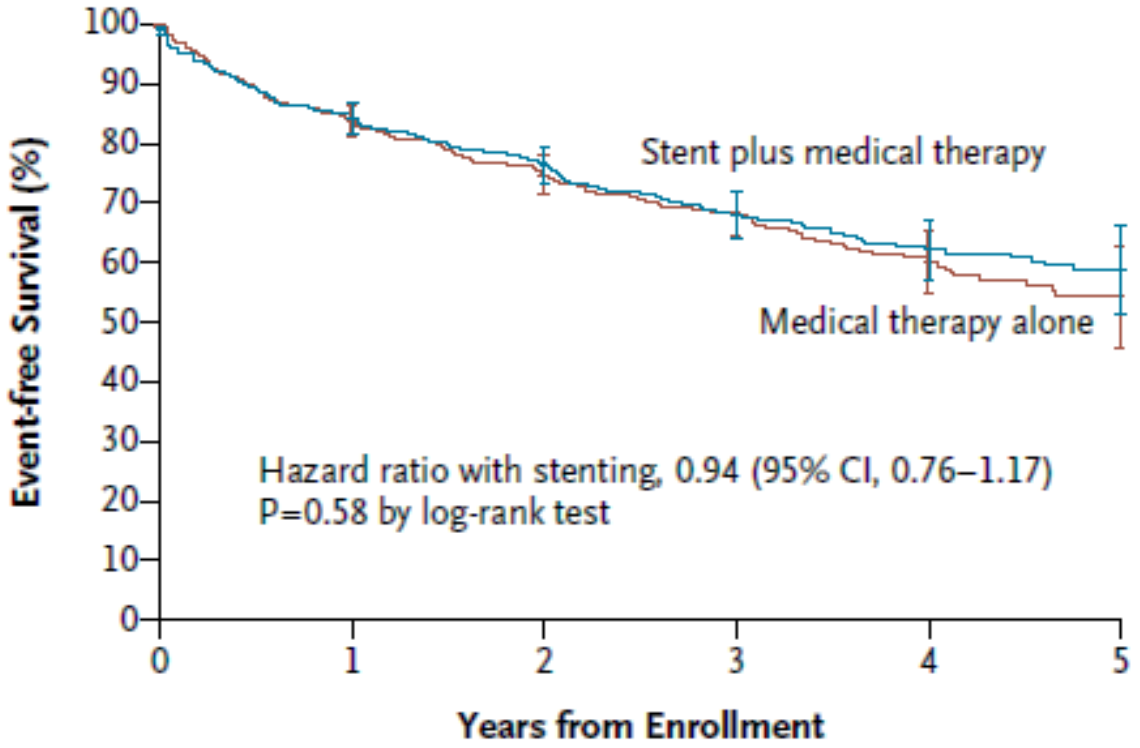


CORAL Primary Endpoint Composite of Clinical Events was Negative

Stent + Medical Therapy 35.1%, 3-years

Medical Therapy 35.8%, 3-years

No benefits by stenosis, BP, or gradients



No. at Risk						
Medical therapy alone	472	371	314	214	115	40
Stent plus medical therapy	459	362	318	224	131	59

Cooper CJ et al. N Engl J Med 2014;370:13-22.

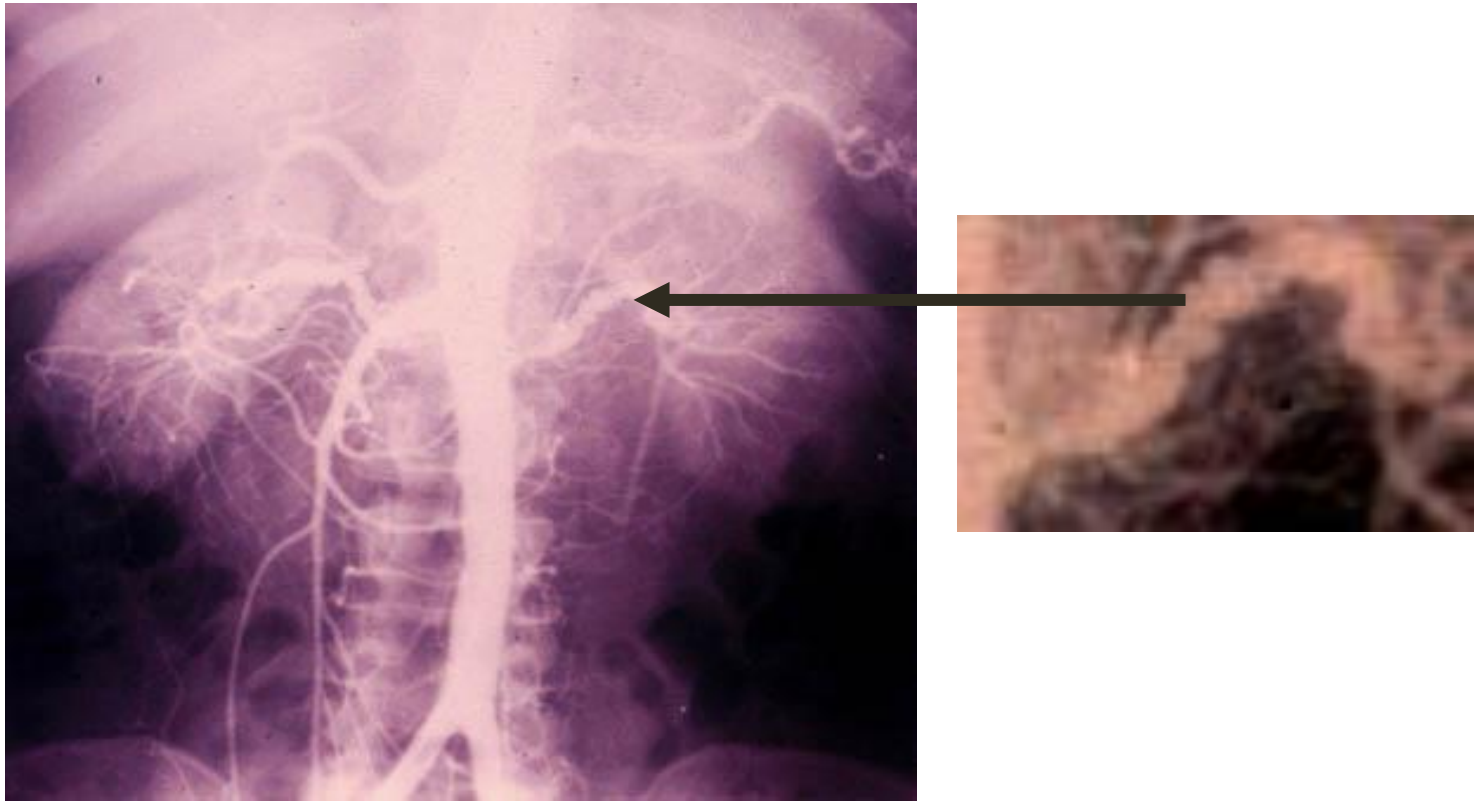
When to intervene in ARAS

- Solitary kidney with increasing creatinine
- Flash pulmonary edema
- Significant high grade bilateral disease with rapidly increasing creatinine
- AKI with ACE/ARB
- Refractory hypertension

- ALWAYS optimize medical management – adequately treat BP, asa, high potency statin and encourage smoking cessation

- **Individualized approach !!**

FMD: Renal Arteriogram



- More common in females
- Ages: 20-50 years
- Bilateral lesions in 60%
- Lesions distal in the renal arteries and branches
- If symptomatic treat with angioplasty and very rarely need stenting
- Can get cervicocranial involvement
- Potentially curable form of hypertension

Physiological mechanisms implicated in changes in renal function following inhibition of SGLT2

a Natriuresis

Tubuloglomerular feedback

- ↓ P_G
- ↑ P_{BOW}
- ↓ Proteinuria

Contraction of plasma volume

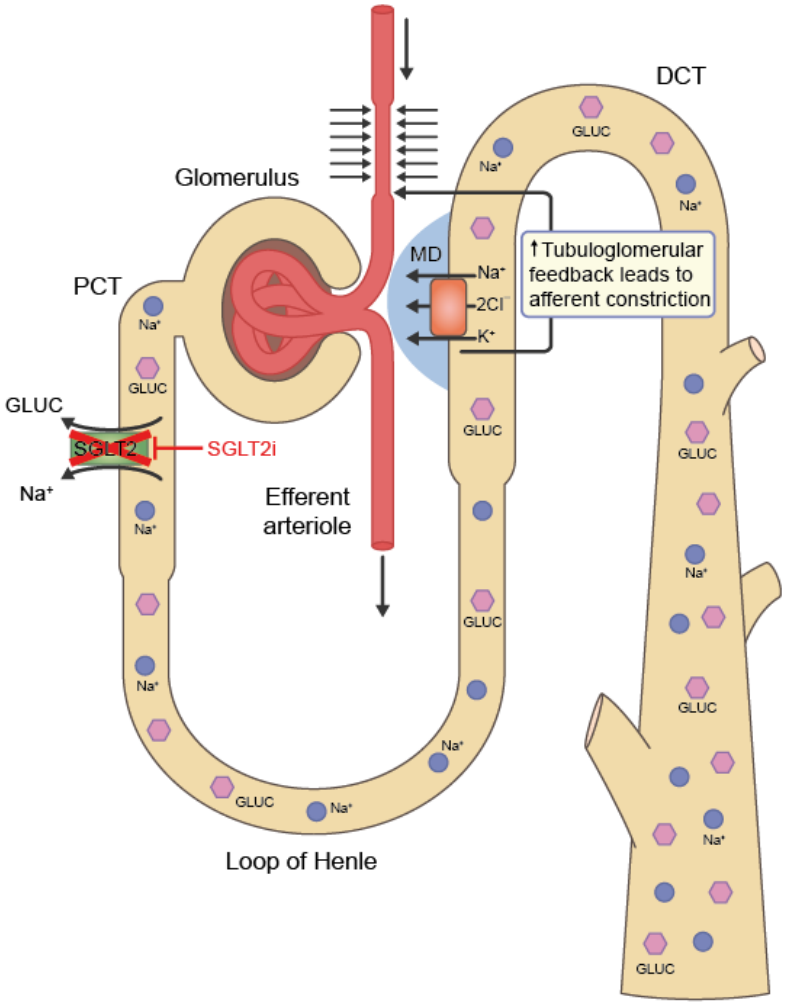
- ↓ Blood pressure
- ↓ Heart failure
- ? Direct/indirect effect on vascular function (e.g. endothelial function)
- ↓ Use of diuretic agents
- ↓ NHE3 activity – additional natriuresis?
- ↑ Erythropoeitin leading to ↑ haematocrit
- ↓ Tubular ischaemia/injury/fibrosis
- ↓ Markers of inflammation
- ↓ Oxidative stress

b Glycosuria

↓HbA_{1c}, ↓Body weight → ↓Metabolic risk and microvascular complication risk

c Natriuresis + Glycosuria

- ↓ Proximal solute reabsorption
- ↓ Energy requirement/utilisation
- ↓ Hypoxia in the kidney



Weight loss: 2-3 kg
BP reduction: 4-6 mm SBP/ 1-2 mm DBP
Albuminuria reduction
CV event reduction
Glucosuria; rare hypoglycemia
Others: volume depletion/ GFR reduction
Frequent AEs: GU infections, Volume depletion

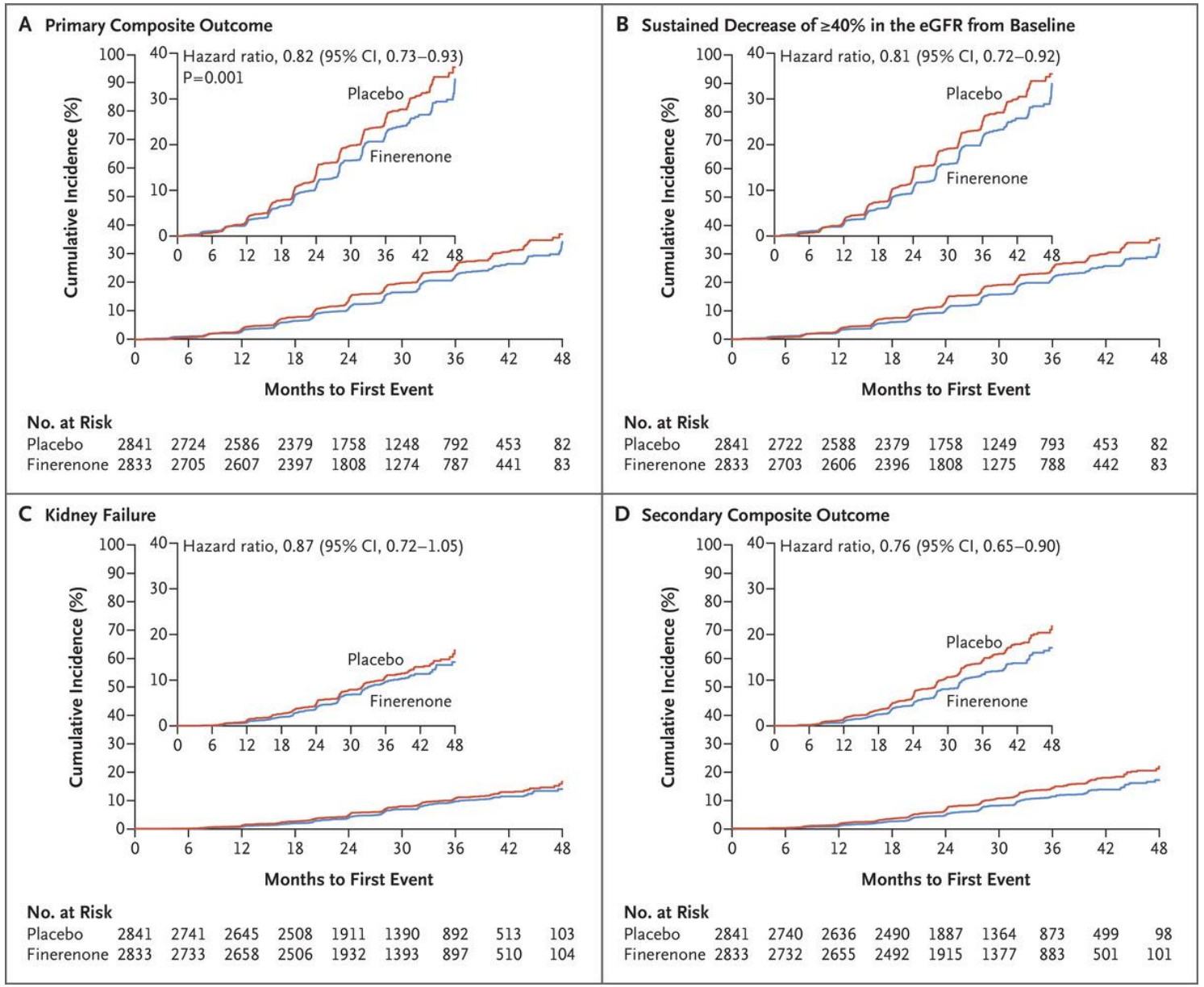
Many patients particularly those with diabetic CKD now taking these drugs so although BP reduction is minimal can cause volume depletion and may need to adjust diuretic doses

Thomas and Cherney (2018) Diabetologia DOI 10.1007/s00125-018-4669-0

Finerenone – New MRA

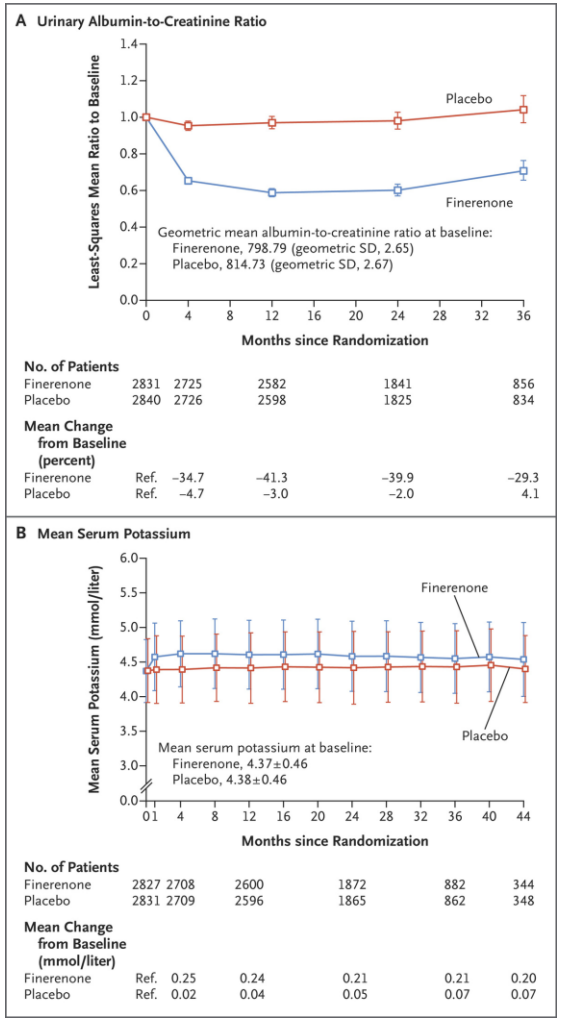
- Finerenone - nonsteroidal, selective MRA
- **Finerenone has been shown to have more potent anti-inflammatory and antifibrotic effects than steroidal MRAs**
- **Smaller effects on serum potassium levels than spironolactone**
- Has NOT been studied in primary aldosteronism
- Finerenone treatment had **modest effects on BP** with reduction in SBP–3.5 mm Hg at month 4 and –2.6 mm Hg at month 24

FIDELIO-DKD - Kidney Outcomes



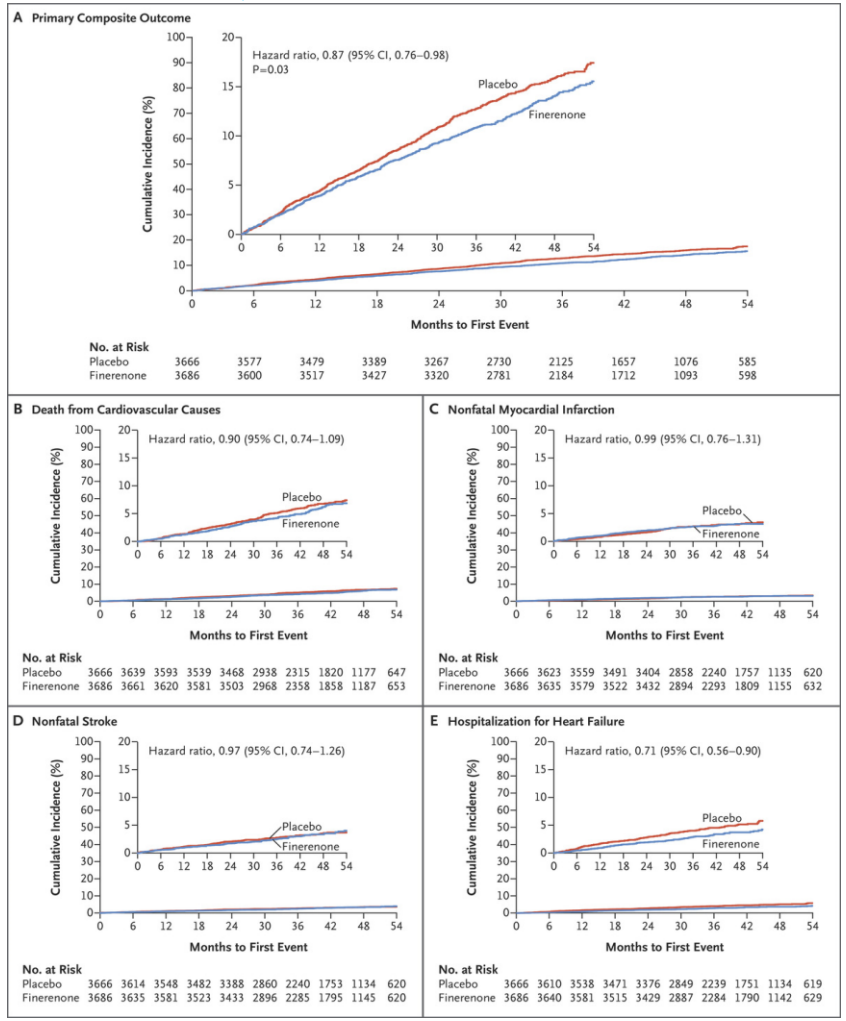
GL Bakris et al. N Engl J Med 2020;383:2219-2229.

Effects on Albuminuria + Serum K over Time



FIDELIO DKD

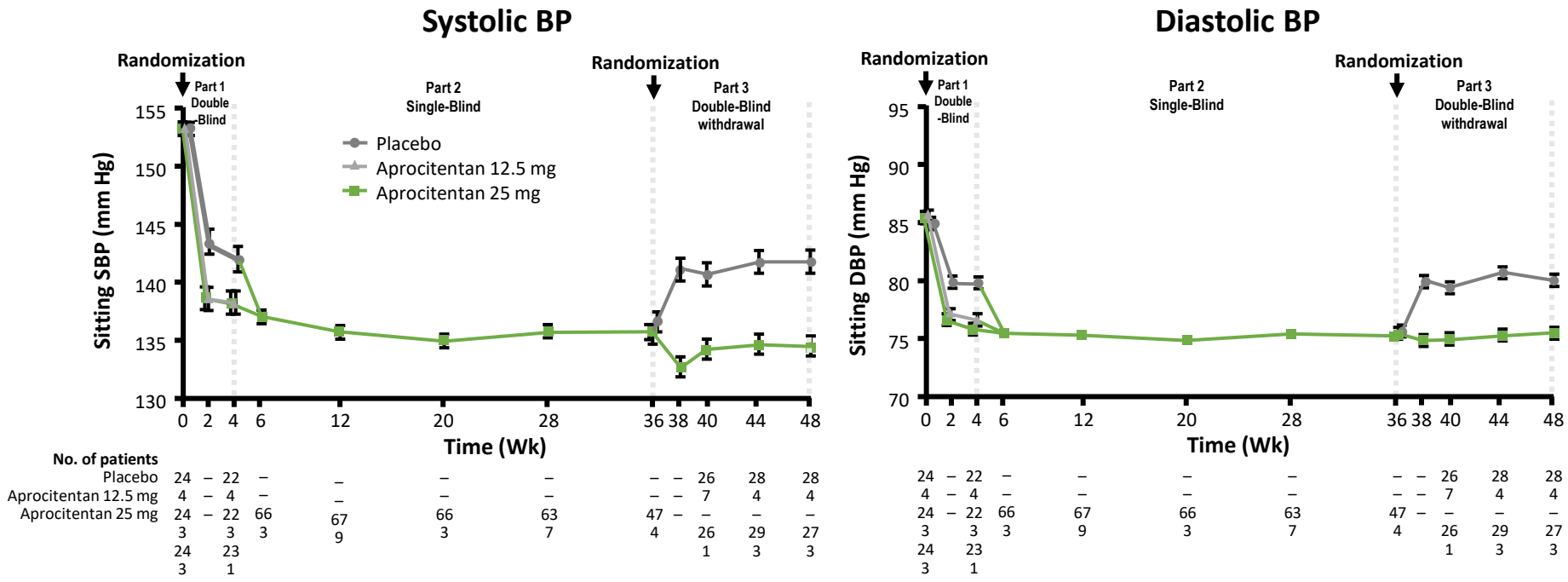
Cardiovascular Outcomes



FIGARO-DKD

GL Bakris et al. N Engl J Med 2020;383:2219-2229.
B Pitt et al. N Engl J Med 2021. DOI: 10.1056/NEJMoa2110956

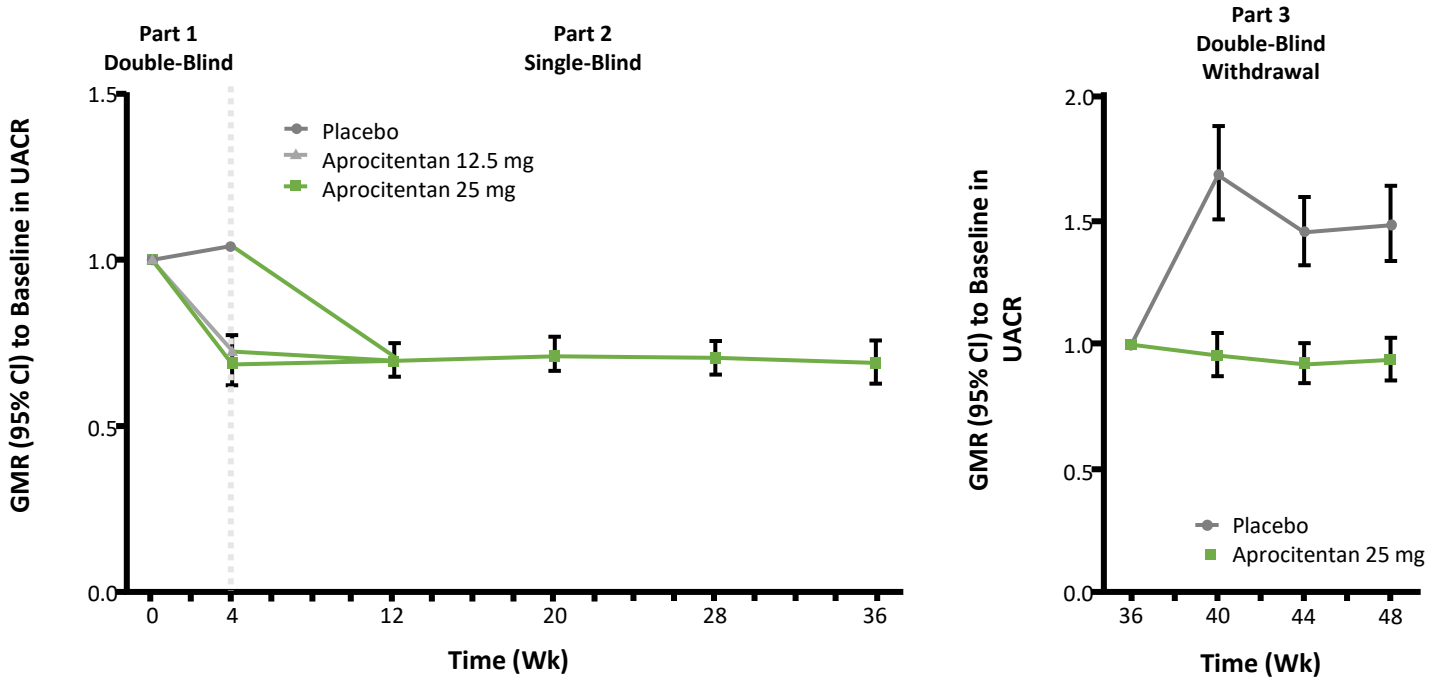
PRECISION: Aprocitentan Phase III Trial



Adverse events included edema or fluid retention, anemia, hepatic disorder

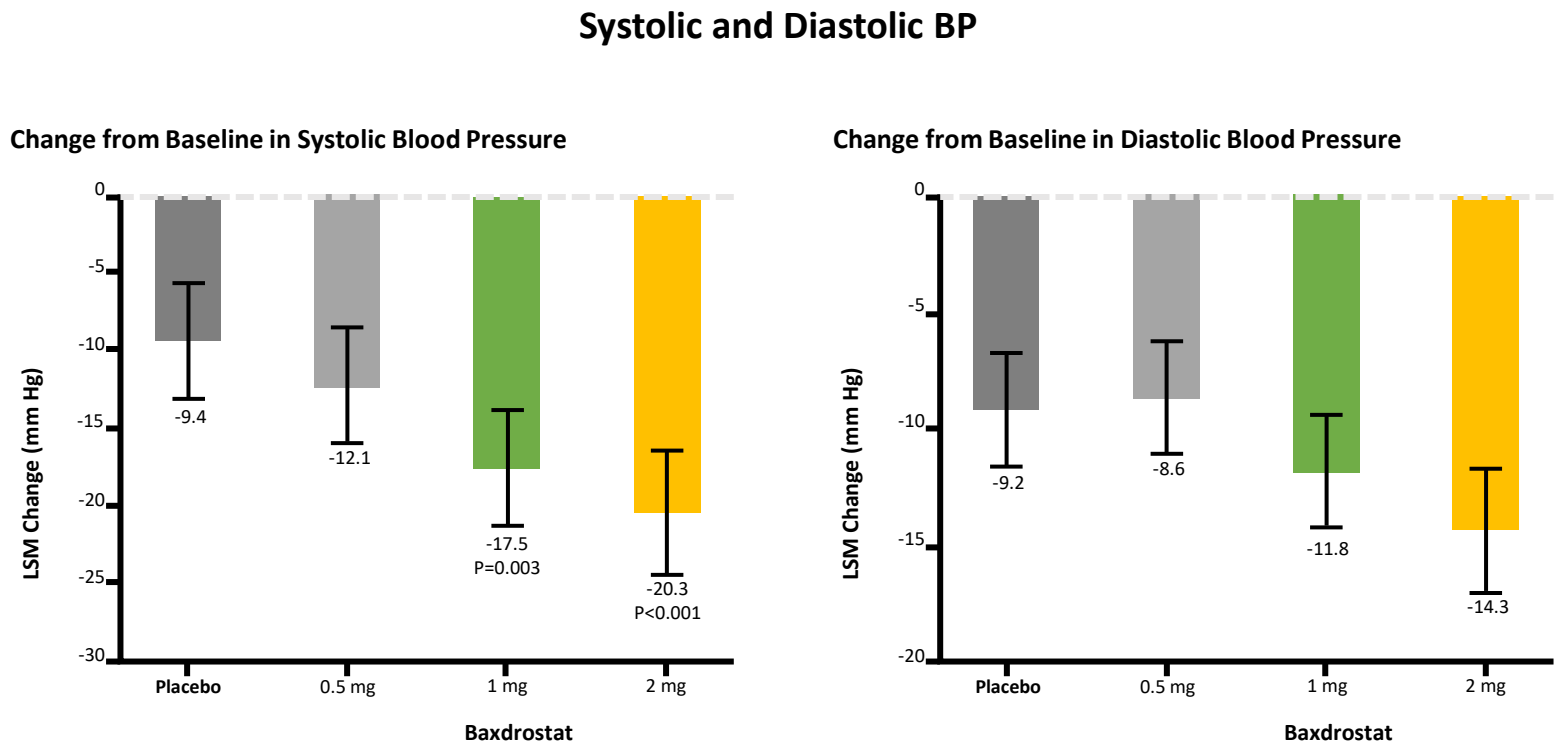
Schlaich. Lancet. 2022;S0140-6736(22)02034-7.

PRECISION: Change in Urine Albumin-Creatinine Ratio (UACR)



Schlaich. Lancet. 2022;S0140-6736(22)02034-7.

Baxdrostat Phase 2 Trial: BrigHTN Trial



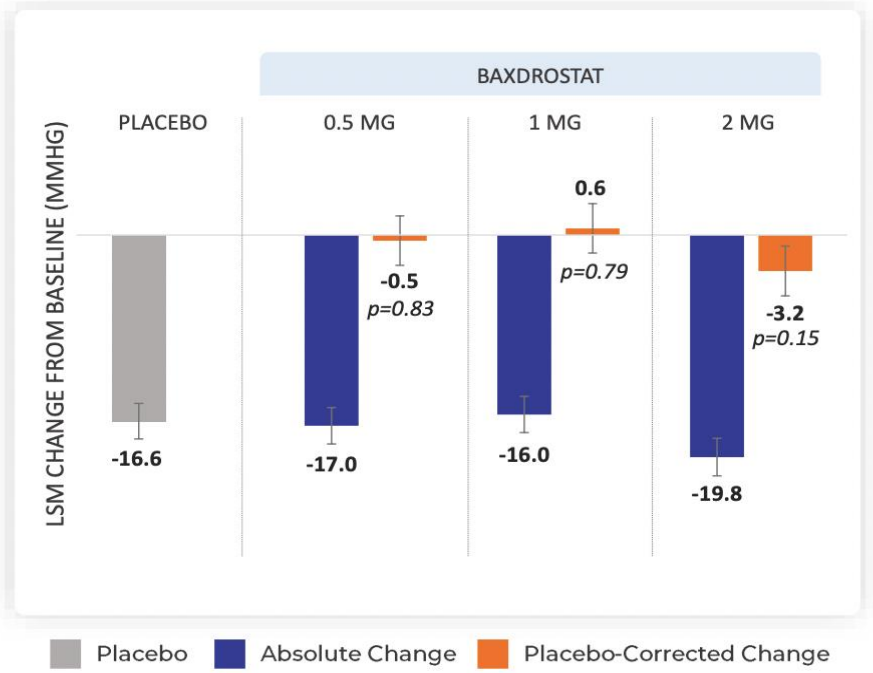
Freeman. N Engl J Med. 2022;doi: 10.1056/NEJMoa2213169.

Baxdrostat Phase 2 Trial: Halo Trial

Primary Endpoint

PLACEBO-CORRECTED CHANGE FROM BASELINE IN MEAN SEATED SBP AT 8 WEEKS

- The primary endpoint of placebo-corrected systolic blood pressure change was not met at any baxdrostat dose
- There was a large decrease in SBP noted in the placebo group



Data are LSM ± SE. The significance of changes from baseline comparing the treatment groups to the placebo group was estimated by an MMRM model. Abbreviations: LSM, least squares mean; SBP, systolic blood pressure.

Randomized 249 patients to baxdrostat 0.5 mg (n = 63), 1 mg (n = 62), 2 mg (n = 60), or placebo (n = 64)

On stable regimen of an ACEi OR ARB, ACEi/ARB + thiazide diuretic, or ACEi/ARB + CCB

Presented at ACC 2023

CLICK TRIAL – Thiazides in advanced CKD

RESEARCH SUMMARY

Chlorthalidone for Hypertension in Advanced Chronic Kidney Disease

Agarwal R et al. DOI: 10.1056/NEJMoa2110730

CLINICAL PROBLEM

Thiazides or thiazide-like diuretics are important for blood-pressure management in patients with essential hypertension, but their safety and efficacy in the treatment of hypertension in patients with advanced chronic kidney disease are poorly understood.

CLINICAL TRIAL

Design: A randomized, double-blind, placebo-controlled trial examined the safety and efficacy of the thiazide-like diuretic chlorthalidone in patients with stage 4 chronic kidney disease and poorly controlled hypertension.

Intervention: 160 patients were randomly assigned to add chlorthalidone (12.5 mg per day, with titration to 50 mg per day as needed) or placebo to their antihypertensive regimen. Patients were receiving an average of 3.4 antihypertensive drugs at baseline. The primary outcome was the change in 24-hour ambulatory systolic blood pressure from baseline to 12 weeks.

RESULTS

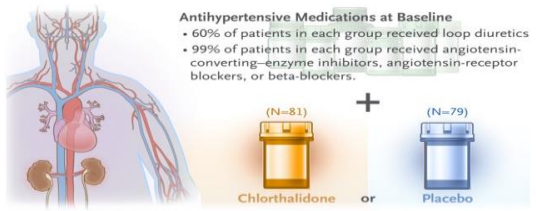
Efficacy: At 12 weeks, the reduction in 24-hour systolic blood pressure was significantly greater in the chlorthalidone group than in the placebo group.

Safety: Adverse events occurred in 91% of patients in the chlorthalidone group and 86% of patients in the placebo group. Increases in serum creatinine level, hypokalemia, hypomagnesemia, hyponatremia, hyperglycemia, hyperuricemia, and dizziness occurred more often with chlorthalidone.

LIMITATIONS AND REMAINING QUESTIONS

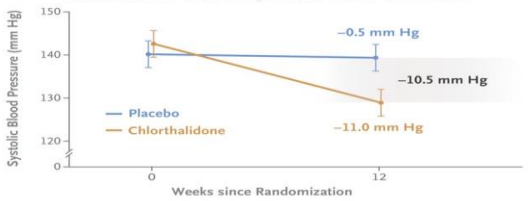
- The number of patients was relatively small, with disproportionately few women, Asian patients, and Hispanic patients.
- Chlorthalidone was associated with a reduction in albuminuria; whether this would translate into cardiovascular and kidney protection in patients with chronic kidney disease is unknown.
- The safest approach to concomitant use of chlorthalidone and loop diuretics in patients with chronic kidney disease remains to be determined, given the possibility of more patients with hypokalemia, increases in serum creatinine level, or both.

Links: Full Article | NEJM Quick Take



Adjusted Change in 24-Hour Ambulatory Systolic Blood Pressure from Baseline to 12 Weeks

Mean difference, −10.5 mm Hg; 95% CI, −14.6 to −6.4; P<0.001

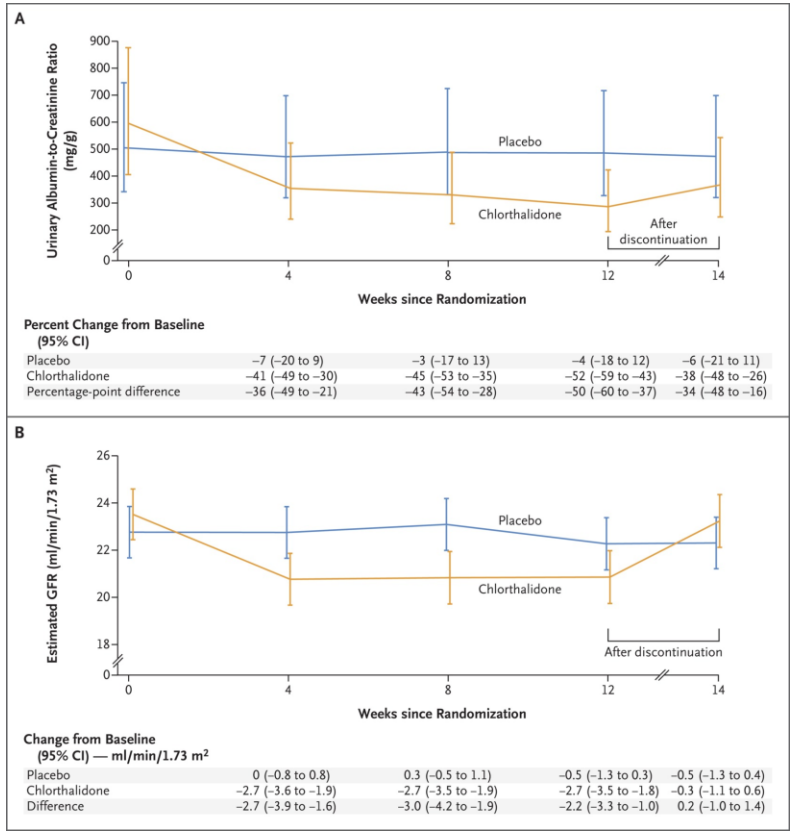


Adverse Events during the Treatment Period

no. with event/total no. (%)	Chlorthalidone	Placebo
Increase in serum creatinine level (>25% from baseline)	33/74 (45)	10/77 (13)
Hypokalemia	8/81 (10)	0
Hypomagnesemia	19/81 (23)	13/79 (16)
Hyponatremia	9/81 (11)	6/79 (8)
Hyperglycemia	13/81 (16)	4/79 (5)
Hyperuricemia	16/81 (20)	7/79 (9)
Dizziness	20/81 (25)	13/79 (16)

CONCLUSIONS

In patients with advanced chronic kidney disease and poorly controlled hypertension, the addition of chlorthalidone to other antihypertensive medications improved blood-pressure control at 12 weeks as compared with placebo.



Percent Change from Baseline (95% CI)

Placebo	−7 (−20 to 9)	−3 (−17 to 13)	−4 (−18 to 12)	−6 (−21 to 11)
Chlorthalidone	−41 (−49 to −30)	−45 (−53 to −35)	−52 (−59 to −43)	−38 (−48 to −26)
Percentage-point difference	−36 (−49 to −21)	−43 (−54 to −28)	−50 (−60 to −37)	−34 (−48 to −16)

Change from Baseline (95% CI) — ml/min/1.73 m²

Placebo	0 (−0.8 to 0.8)	0.3 (−0.5 to 1.1)	−0.5 (−1.3 to 0.3)	−0.5 (−1.3 to 0.4)
Chlorthalidone	−2.7 (−3.6 to −1.9)	−2.7 (−3.5 to −1.9)	−2.7 (−3.5 to −1.8)	−0.3 (−1.1 to 0.6)
Difference	−2.7 (−3.9 to −1.6)	−3.0 (−4.2 to −1.9)	−2.2 (−3.3 to −1.0)	0.2 (−1.0 to 1.4)

Changes in Urinary Albumin-to-Creatinine Ratio and Estimated GFR in the Trial Groups over the Trial Period

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Zilebesiran, an RNA Interference Therapeutic Agent for Hypertension

Desai AS et al. DOI: 10.1056/NEJMoa2208391

CLINICAL PROBLEM

Nearly half of patients with hypertension do not reach guideline-recommended blood-pressure targets. Zilebesiran is an investigational RNA interference therapeutic agent that inhibits the production of angiotensinogen, the precursor of angiotensin, which plays a key role in the pathogenesis of hypertension.

CLINICAL TRIAL

Design: A four-part, multicenter, phase 1 study assessed the safety and blood-pressure–lowering effects of zilebesiran in adults ≤65 years of age with treated or untreated hypertension.

Intervention: 107 patients were enrolled. In Part A, patients were randomly assigned to a single subcutaneous dose of zilebesiran (at one of seven doses ranging from 10 to 800 mg) or placebo. In Part B, zilebesiran (800 mg) or placebo was administered under low- and high-salt dietary conditions, and in Part E, irbesartan was added to zilebesiran (800 mg). (Part C was removed during a protocol amendment, and Part D is ongoing.) The primary end point was the frequency of adverse events.

RESULTS

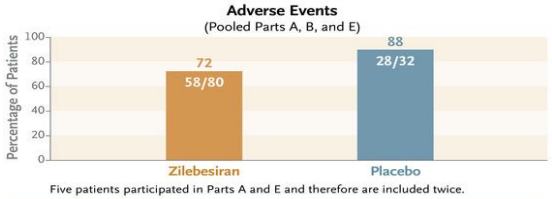
Safety: Overall, adverse events were not more frequent with zilebesiran than with placebo. Five zilebesiran recipients had mild, transient injection-site reactions. No patient received interventions for hypotension, hyperkalemia, or worsening of renal function.

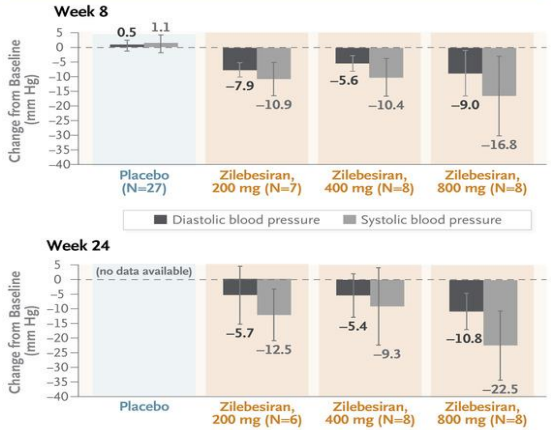
Efficacy: In Part A, single doses of zilebesiran of ≥200 mg were associated with dose-dependent decreases in blood pressure that were apparent by week 8 and were sustained for up to 24 weeks. In Part B, a high-salt diet appeared to attenuate the blood-pressure–lowering effects of zilebesiran. In Part E, irbesartan appeared to enhance the effects of zilebesiran.

LIMITATIONS AND REMAINING QUESTIONS

- The efficacy end points were exploratory.
- The study was too small and short to fully assess safety.
- Whether zilebesiran has the teratogenic effects of other renin–angiotensin system inhibitors is unknown.

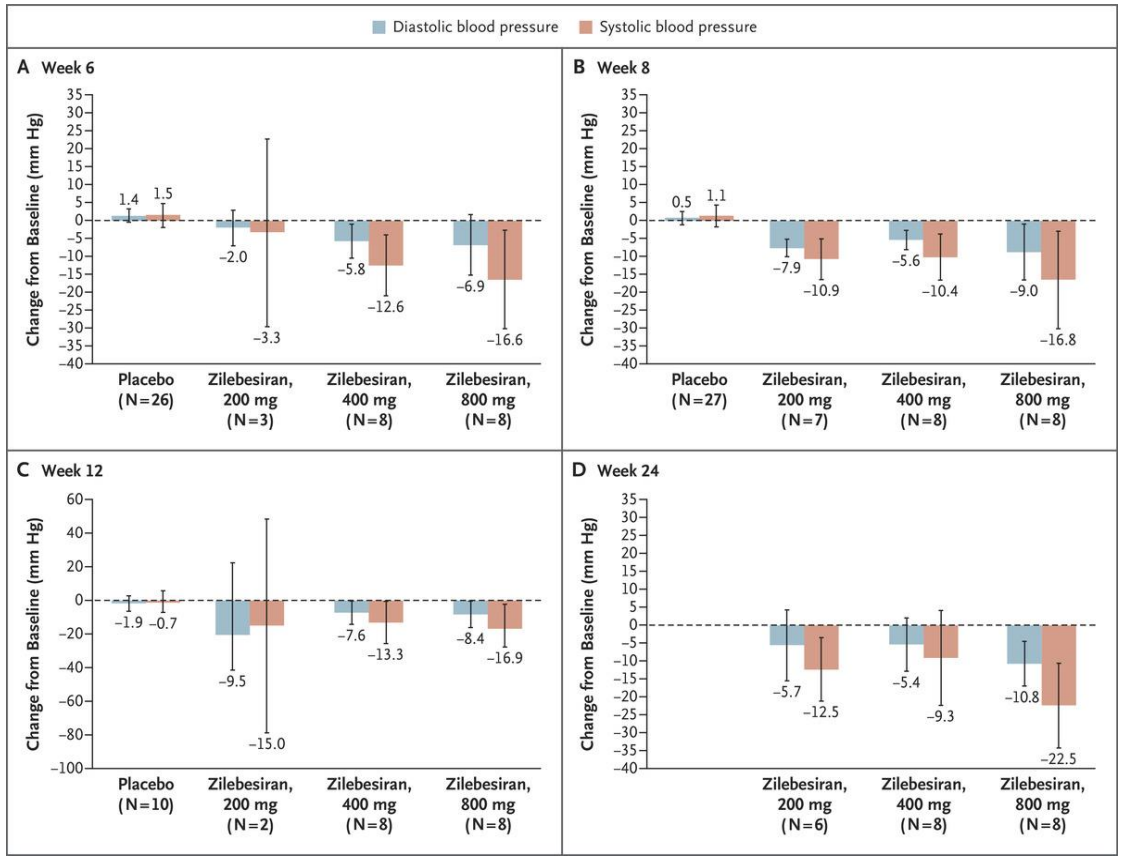
Links: Full Article | NEJM Quick Take | Science behind the Study





CONCLUSIONS

In patients with hypertension, the investigational RNA interference therapeutic agent zilebesiran was associated with mild injection-site reactions and led to dose-dependent decreases in blood pressure that were sustained at 24 weeks of follow-up.



Decreases in Systolic and Diastolic Blood Pressure a after Single Doses of Zilebesiran

Aldosterone Synthase Inhibition With Lorundrostat for Uncontrolled Hypertension: The Target-HTN Randomized Clinical Trial

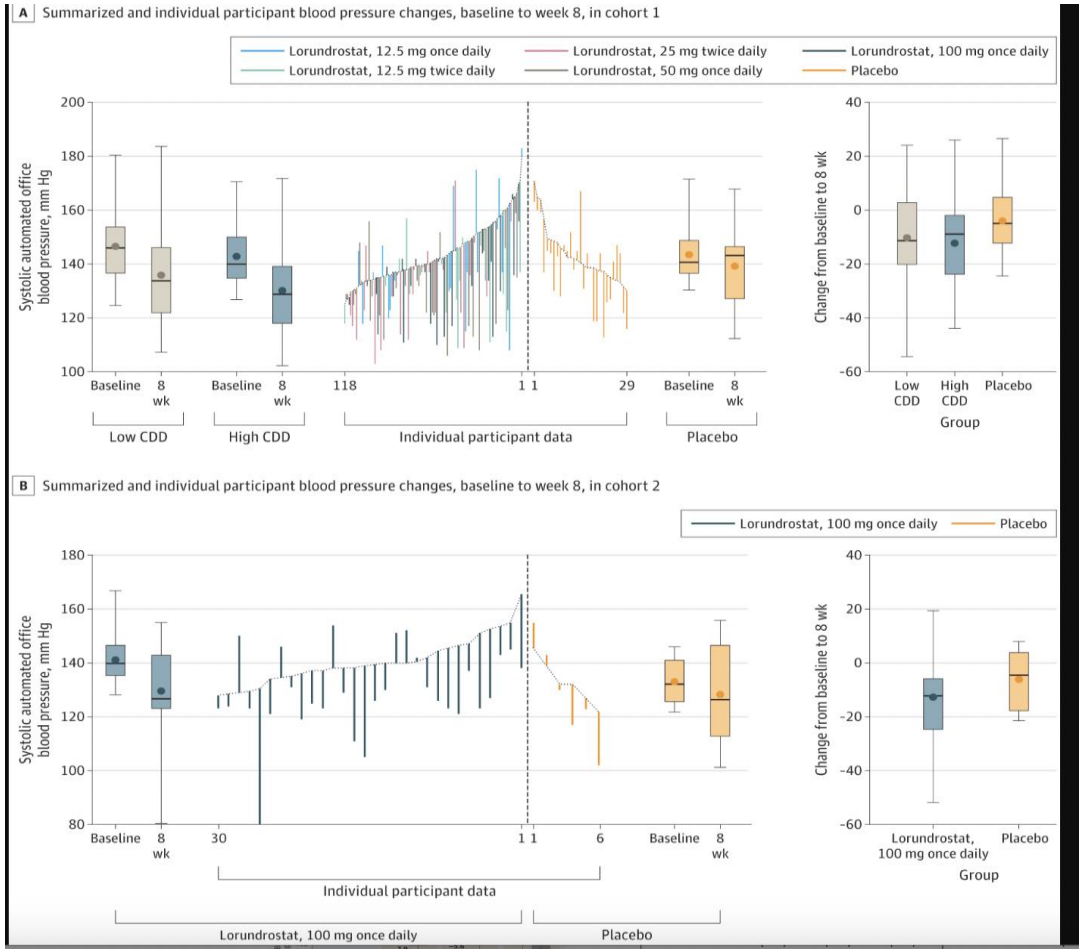


Table 2. Primary and Secondary Efficacy End Points[a]

End points	Cohort 1 (PRA ≤1.0 ng/mL/h) Lorundrostat 100 mg once daily (n = 25)	Lorundrostat 50 mg once daily (n = 28)	Lorundrostat 25 mg twice daily (n = 28)	Lorundrostat 12.5 mg twice daily (n = 19)	Lorundrostat 12.5 mg once daily (n = 19)	Placebo (n = 29)	Exploratory cohort 2 (PRA >1.0 ng/mL/h)[b] Lorundrostat, 100 mg once daily (n = 31)	Placebo (n = 6)
Primary end point								
Automated office SBP, baseline to wk 8								
Baseline SBP, mean (SD), mm Hg	143.8 (12.0)	141.8 (10.9)	140.9 (9.6)	144.6 (10.5)	147.1 (11.6)	142.7 (10.2)	140.4 (8.6)	132.9 (8.4)
Wk 8 SBP, mean (SD), mm Hg	131.3 (14.1)	128.6 (13.7)	131.3 (16.6)	131.9 (12.9)	140.8 (22.0)	139.1 (14.2)	129.3 (15.4)	128.3 (18.9)
Change in SBP, least-squares mean (SE), mm Hg	−11.9 (2.8)	−13.7 (2.7)	−11.1 (2.7)	−11.3 (3.2)	−5.6 (3.2)	−4.1 (2.6)	−11.4 (2.5)	
Difference from placebo in SBP change, least-squares mean, (90% CI), mm Hg	−7.8 (−14.1 to −1.5)	−9.6 (−15.8 to −3.4)	−7.0 (−13.1 to −0.8)	−7.2 (−14.0 to −0.4)	−1.5 (−8.3 to 5.3)			
P value	.04	.01	.06	.08	.71			
Secondary end point								
Automated office DBP, baseline to wk 8								
Baseline DBP, mean (SD), mm Hg	78.9 (9.6)	84.9 (6.4)	78.9 (8.0)	81.6 (7.6)	82.4 (10.7)	83.4 (8.8)	78.1 (7.6)	78.3 (7.6)
Wk 8 DBP, mean (SD), mm Hg	73.0 (9.4)	76.8 (9.8)	75.4 (13.1)	75.2 (10.1)	81.4 (17.2)	81.3 (9.4)	72.2 (8.4)	76.2 (11.0)
Change in DBP, least-squares mean (SE), mm Hg	−5.8 (1.8)	−7.1 (1.7)	−4.1 (1.7)	−5.5 (2.0)	−3.8 (2.0)	−1.6 (1.7)	−5.6 (1.4)	
Difference from placebo in DBP change, least-squares mean, (90% CI), mm Hg	−4.1 (−8.1 to −0.1)	−5.5 (−9.4 to −1.5)	−2.5 (−6.4 to 1.4)	−3.8 (−8.2 to 0.5)	−2.1 (−6.5 to 2.2)			
P value	.09	.02	.30	.14	.42			

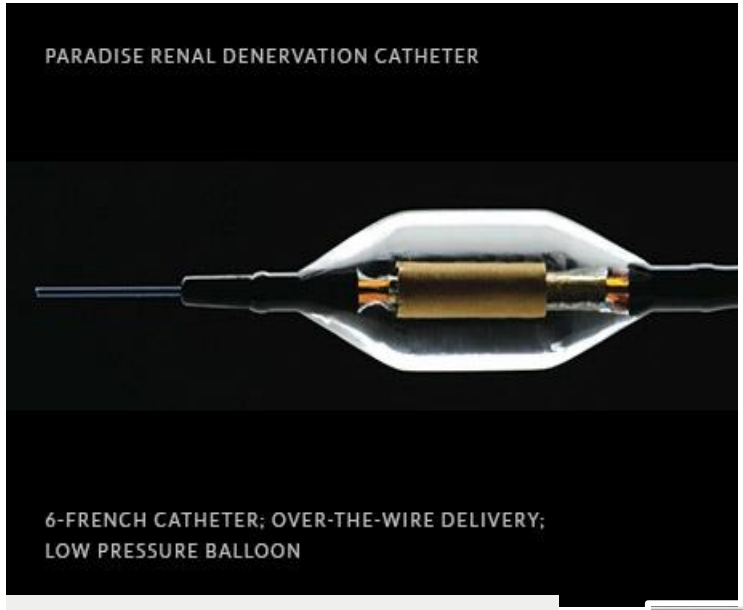
Table 3. Adverse Events and Serum Potassium Changes

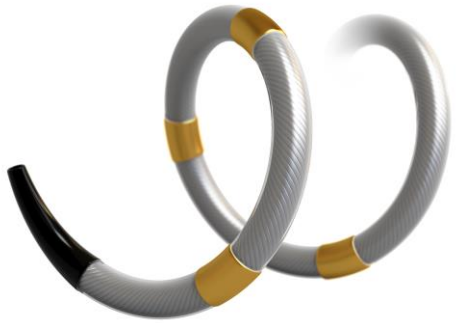
Measures	Cohort 1 (PRA ≤1.0 ng/mL/h) Lorundrostat 100 mg once daily (n = 30)	Lorundrostat 50 mg once daily (n = 28)	Lorundrostat 25 mg twice daily (n = 30)	Lorundrostat 12.5 mg twice daily (n = 22)	Lorundrostat 12.5 mg once daily (n = 23)	Placebo (n = 30)	Exploratory cohort 2 (PRA >1.0 ng/mL/h) Lorundrostat, 100 mg once daily (n = 31)	Placebo (n = 6)
Participants with any serious adverse event, No. (%)	0	0	0	0	2 (9)[a]	0	1 (3)[b]	0
Participants with any adverse event, No. (%)[c]	17 (57)	12 (43)	20 (67)	13 (59)	16 (70)	12 (40)	19 (61)	1 (17)
Participants with hypotension, No. (%)	1 (3)	0	0	1 (5)	0	0	1 (3)	0
Potassium-related events[d]								
Change from baseline in serum potassium level, mean (SD), mmol/L	0.29 (0.59)	0.25 (0.36)	0.34 (0.46)	0.32 (0.53)	0.31 (0.44)	0.03 (0.37)	0.21 (0.54)	−0.05 (0.28)
Participants with serum potassium level 5.6-6.0 mmol/L, No. (%)	5 (16)	1 (4)	2 (7)	2 (9)	3 (13)	0	2 (6)	0
Participants with serum potassium level 6.1-6.5 mmol/L, No. (%)	0	0	1 (3)	1 (5)	1 (4)	0	1 (3)	0
Participants with serum potassium level >6.5 mmol/L, No. (%)	1 (3)	1 (4)	0	0	0	0	0	0

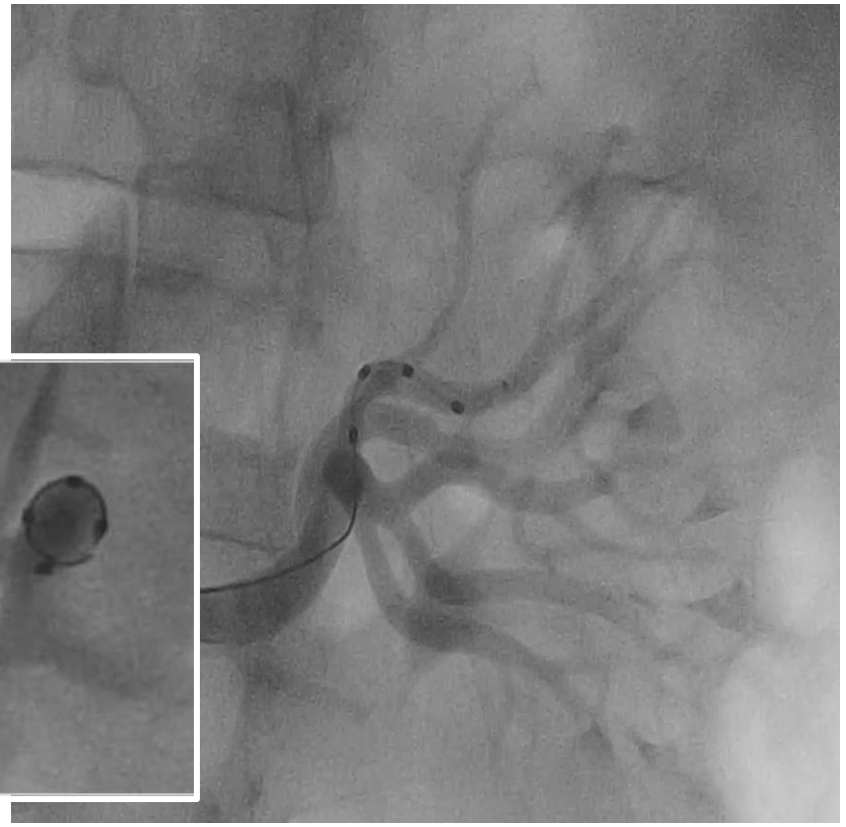
Abbreviation: PRA, plasma renin activity.

unlikely related, unrelated, possibly related, or definitely related. Criteria for deeming possibly or definitely

Renal Denervation (RDN)

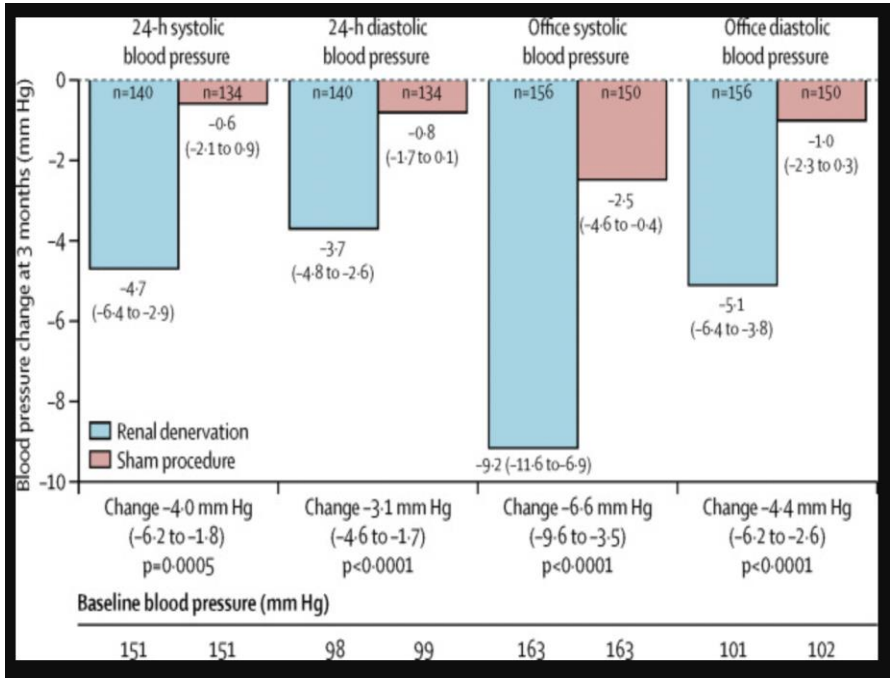




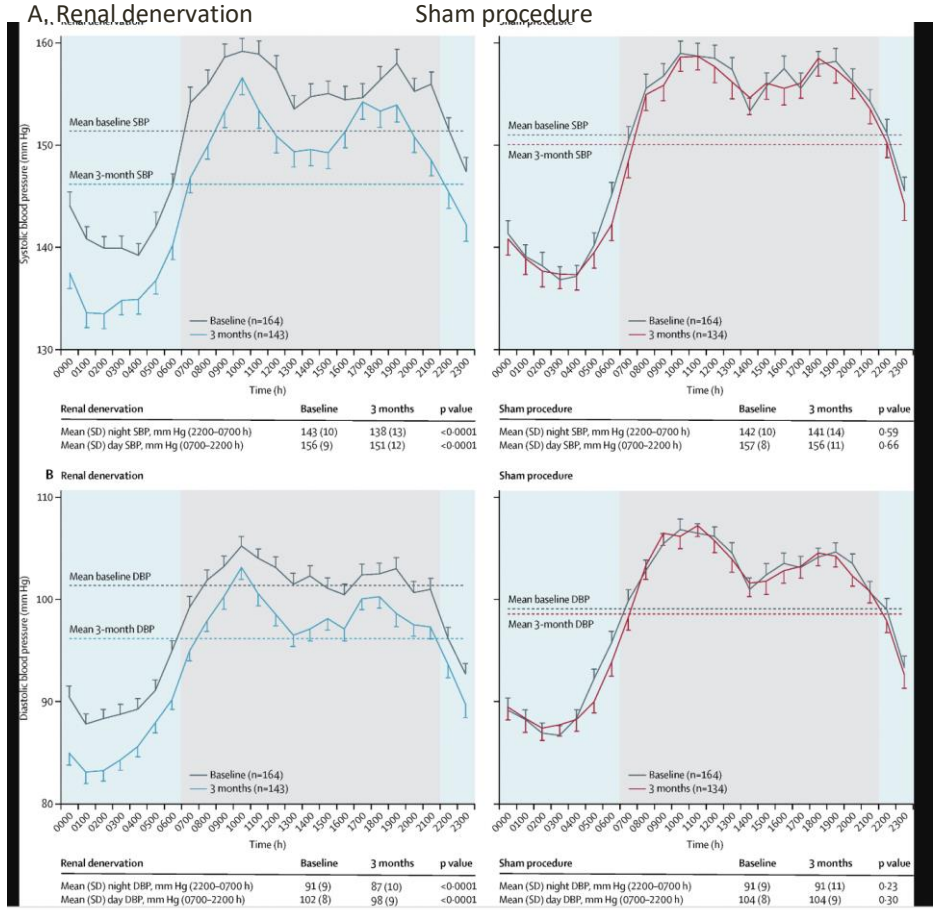


Spyral OFF MED study

Changes in 24-h and office systolic and diastolic blood pressure from baseline to 3 months

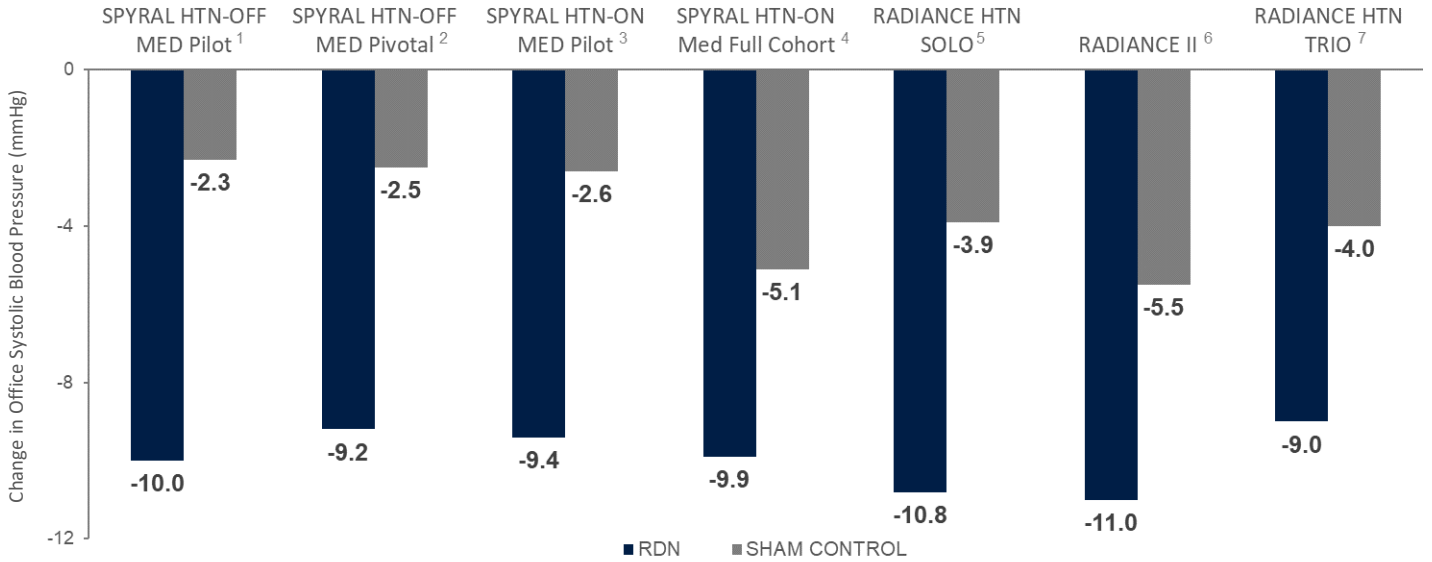


24-h ambulatory SBP (A) and DBP (B) at baseline and 3 months for renal denervation and sham control groups in the overall population



With and without medications

Multiple sham controlled RCT's demonstrated effectiveness of RDN



N	38	42	166	165	38	42	206	131	74	72	150	74	69	67
Follow-up Duration (months)	3		3		6		6		2		2		2	
Baseline SBP (mmHg)	162	161	163	163	165	164	163	163	150	150	156	154	162	164
ΔSBP between groups (mmHg)	**-7.1**		**-6.6**		**-6.8**		**-4.9**		**-6.3**		**-5.4**		**-7.0**	
P*	**0.021**		**<0.0001**		**0.021**		**0.001**		**0.001**		**<0.0035**		**0.037**	

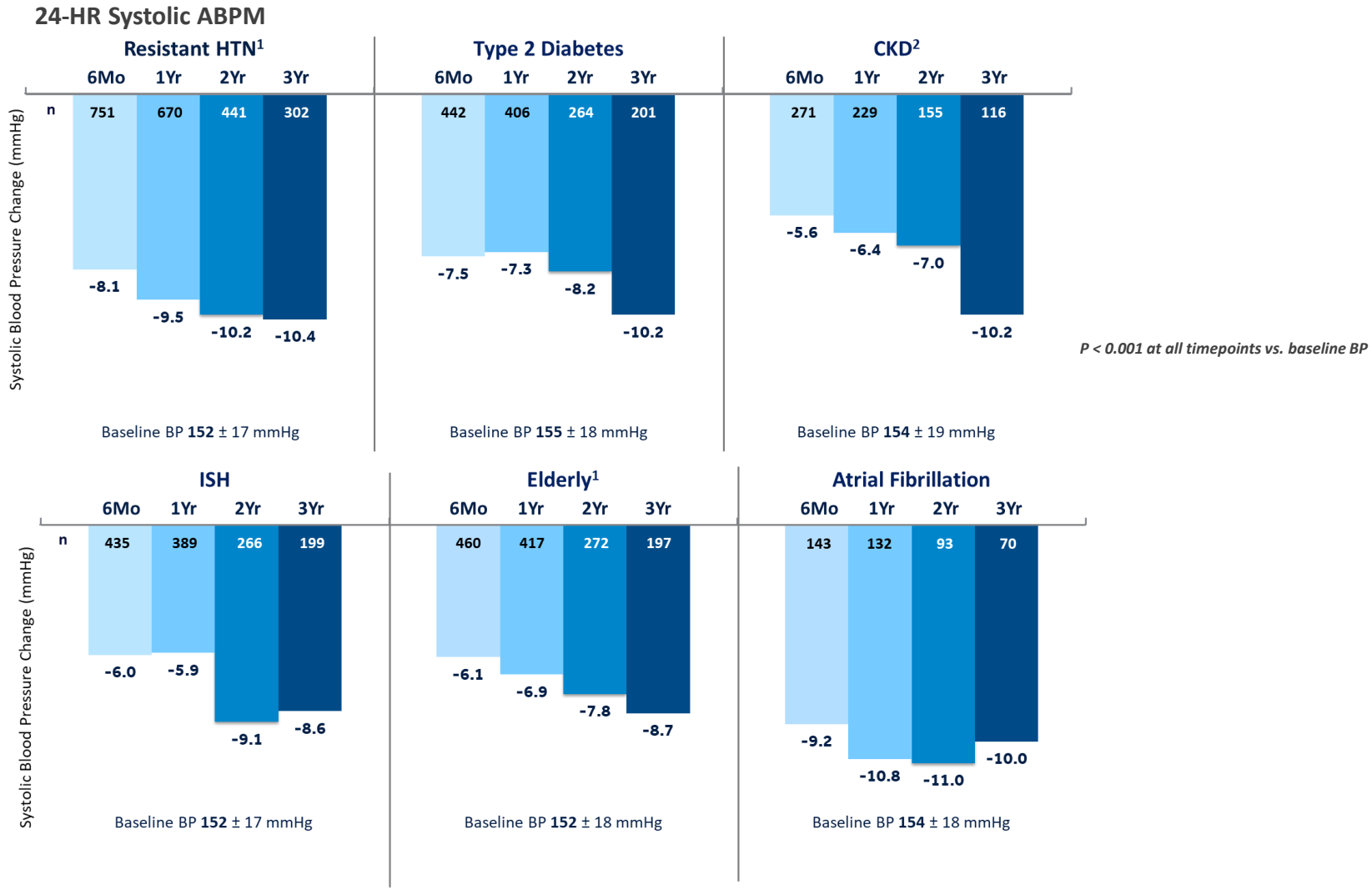
*Baseline (ANCOVA) adjusted

1. Townsend R, et al. *Lancet*. 2017
2. Böhm M, et al. *Lancet*. 2020
3. Kandzari et al. *Lancet*. 2018
4. Kandzari AHA 2022.
5. Azizi et al. *Lancet*. 2018
6. Kirtane TCT 2022.
7. Azizi et al. *Lancet*. 2021

WHO is a candidate for RDN ?

Renal Denervation Reduced BP in a Variety of Patient Subgroups

BP Change in High-Risk Subgroups Similar to Overall Cohort in GSR



P < 0.001 at all timepoints vs. baseline BP

GSR data is combined Symplicity Flex and Symplicity Spyral
Mahfoud F, et al. *J Am Coll Cardiol*. 2020;75:2879-2888.

[1] Resistant hypertension defined as OSBP>150 mmHg, ≥3 anti-hypertensive medications.
[2] CKD defined as eGFR <60ml/min/1.73m2

SPYRAL HTN ON and OFF-MED Safety Results

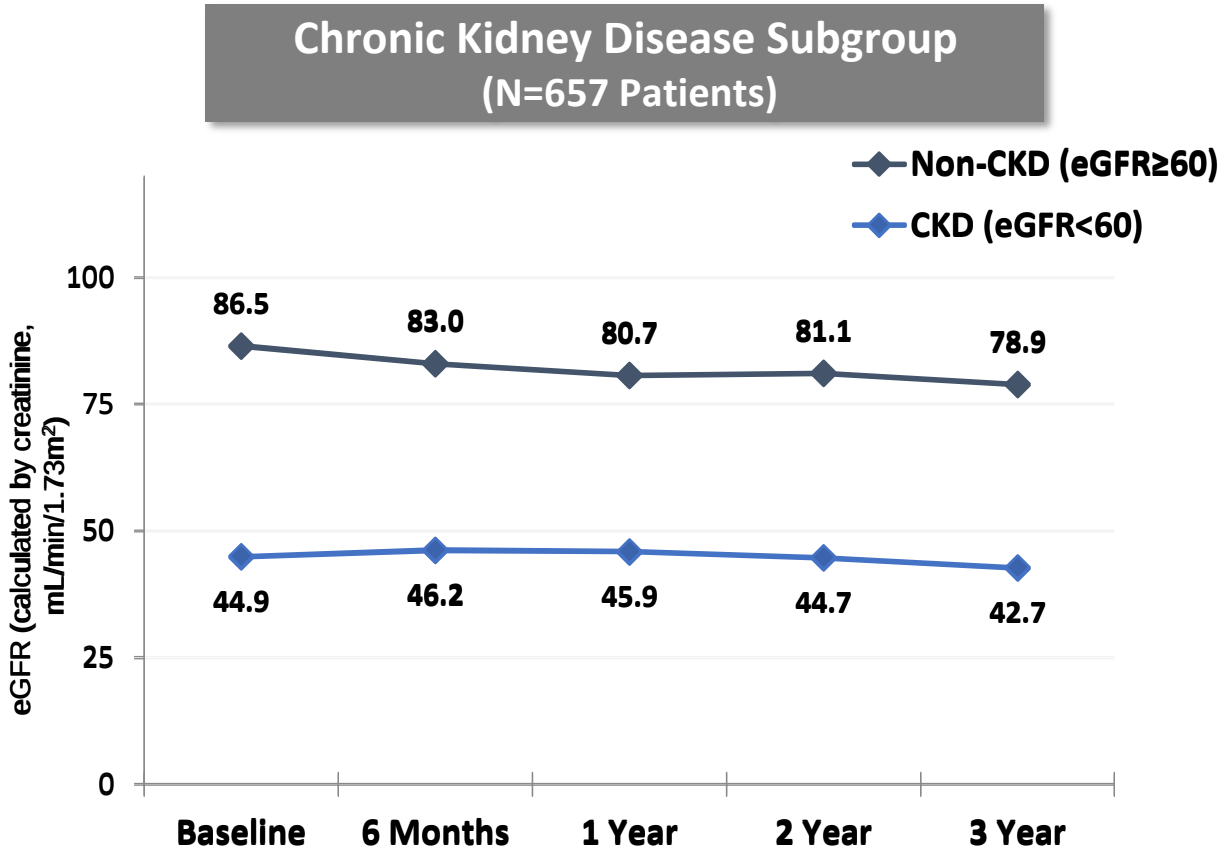
No New Events of Stenosis (> 70%) Detected

n (%)	SPYRAL HTN-OFF MED PIVOTAL[1] 3M Post Procedure		SPYRAL HTN-ON MED[2] 3M and 6M Post Procedure	
	RDN (n = 165)	Sham Control (n = 165)	RDN (n = 38)	Sham Control (n = 42)
Major Adverse Events	1 (0.6%)	0	0	0
Death	0	0	0	0
New-onset end-stage renal disease	0	0	0	0
Sign. embolic event resulting in end-organ damage	0	0	0	0
Renal artery perforation or dissection requiring intervention	0	0	0	0
Vascular complications	0	0	0	0
Hospitalization for hypertensive crisis/emergency	1 (0.6%)	0	0	0
New stroke	0	1 (0.6%)	0	0
Major bleeding (TIMI*)	0	0	0	0
Serum creatinine elevation >50%	0	0	0	0
New myocardial infarction	0	0	0	0

* TIMI definition: intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, a ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of procedure.

[1] Böhm M, et al. *Lancet*. 2020;395:1444-1451 [2] Kandzari DE, et al. *Lancet*. 2018;391:2346-2355

Global SYMPLICITY Registry: Renal Function Over 3 Years

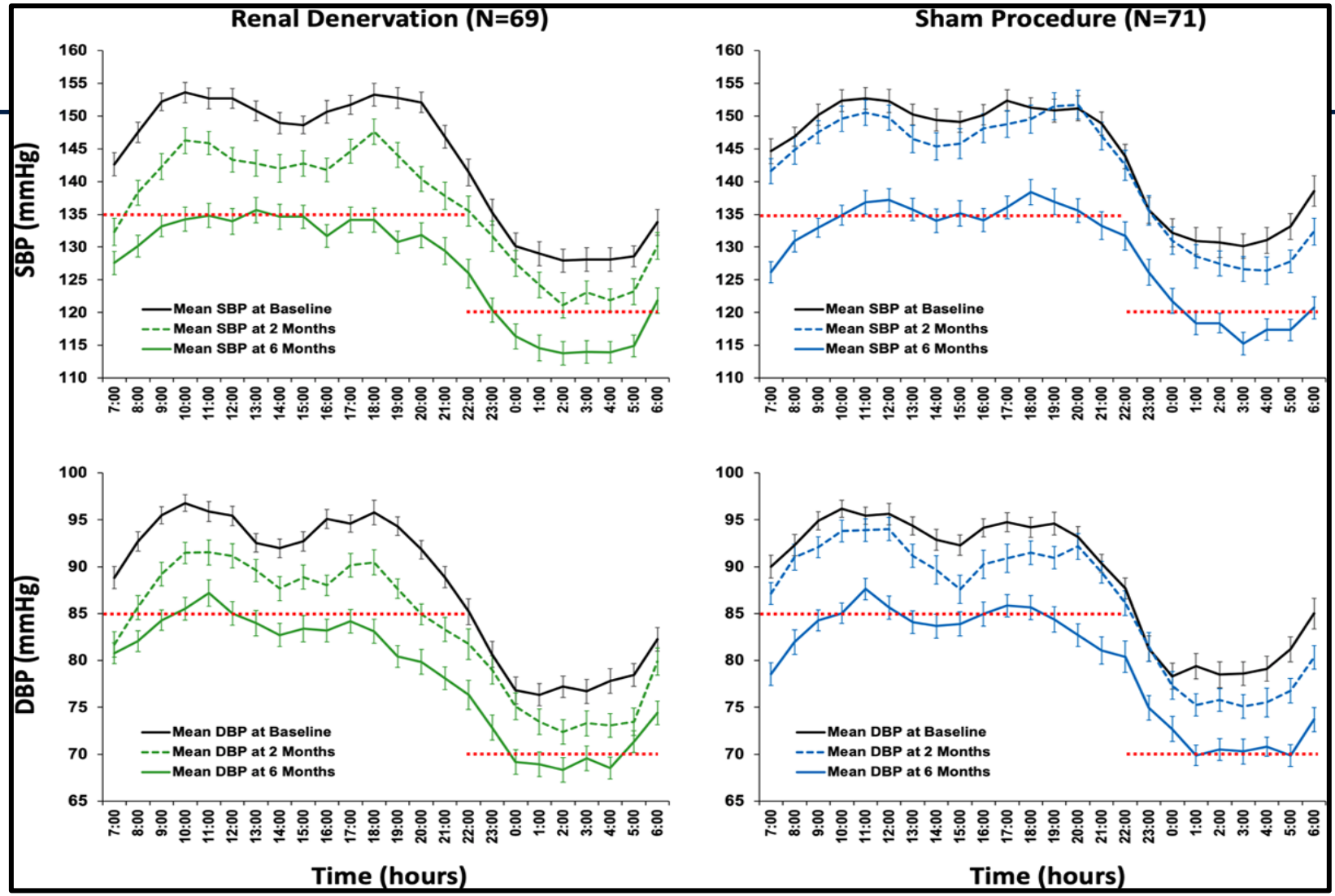


Non-CKD	N=1926	1128	1100	804	637
CKD	N=657	395	359	274	208

*$P < 0.001$ vs. baseline eGFR

[1]Mahfoud F, et al. Presented at ACC 2019 and Gonçalves P at PCR E-course 2020.

Six-Month Results of Treatment-Blinded Medication Titration for Hypertension Control After Randomization to Endovascular Ultrasound Renal Denervation or a Sham Procedure in the RADIANCE-HTN SOLO Trial



24 hr Twenty-four–hour ambulatory profiles at baseline, 2, and 6 months in the renal denervation group (left) and the sham group (right) in the analysis population. Systolic blood pressure (SBP) is shown on the top and diastolic blood pressure (DBP) on the bottom; error bars represent SE. Red dotted lines show the upper limit of normal daytime and nighttime systolic (135 and 120 mm Hg, respectively; top) and diastolic blood pressure (85 and 70 mm Hg, respectively; bottom).

- Home Advisory Committees Circulatory System Devices Panel of the Medical Devices Advisory Committee Meeting Announcement
- ADVISORY COMMITTEE MEETING
- August 22-23, 2023
- Final FFDA may come in soon then need to add the final report- these are just advisory

https://www.fda.gov/advisory-committees/advisory-committee-calendar/august-22-23-2023-circulatory-system-devices-panel-medical-devices-advisory-committee-meeting

US FDA advisory panel voted in support of premarket approval application Recor Medical Paradise Ultrasound Renal Denervation (RDN) system. 8/22/23

- Reviewing data 3 different trials—RADIANCE II, RADIANCE-HTN SOLO and RADIANCE-HTN TRIO—
- Count of 12 to 0 that device safe to use for patients with uncontrolled HTN.
- Count of 8 to 3 (1 member abstain), system effective for the treatment of these patients.
- Count of 10 to 2 that benefits of the Paradise Ultrasound RDN system outweigh any potential risks.

Circulatory System Devices Panel of the Medical Devices Advisory Committee **| 23 AUG 2023**

US FDA advisory panel voted not to endorse premarket approval application Medtronic Symplicity Spyral Renal Denervation (RDN) System. 8/23/23

- Reviewing evidence SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED clinical trials.
- Count of 13 to 0 device was safe to use with uncontrolled HTN
- Count of 7 to 6 device was effective for treating intended population.
- Determining whether RDN system's benefits outweighed any potential risks, count of 6 to 6—(I abstain); chair a no, creating a final vote of 6 to 7

Circulatory System Devices Panel of the Medical Devices Advisory Committe **| 24 AUG 2023**

Use of renal denervation

2023 ESH Guidelines for the Management of Arterial HTN

Recommendations and statements	CoR	LoE
RDN can be considered as a treatment option in patients an eGFR >40 ml/min/1.73m^2 who have uncontrolled BP despite the use of antihypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.	II	B
RDN can be considered as an additional treatment option in patients with resistant hypertension if eGFR is >40 ml/min/1.73m^2.	II	B
Selection of patients to whom RDN is offered should be done in a shared decision-making process after objective and complete patient's information.	I	C
Renal denervation should only be performed in experienced specialized centers to guarantee appropriate selection of eligible patients and completeness of the denervation procedure.	I	C

Mancia(Chairperson) G, Kreutz(Co-Chair) R, Brunström M, et al. *Journal of Hypertension*. 2023;Publish Ahead of Print.

Conclusion

- Most resistant hypertension is due to drug management issues (lack of adequate regimen, non-compliance, side effects, physician apathy)
- Clinician empathy increases patient trust, motivation, and adherence to therapy
- **Once daily dosing, combination therapies, diuretics in CKD**
- Secondary hypertension only accounts for 5-10 % of hypertension
- Hyperaldosteronism is present in approximately 20-30 % of patients with resistant hypertension
- Some of the potential new options on the horizon include RDN, endothelin antagonists, aldosterone synthase inhibitors, SGLT2 inhibitors and non-steroidal MRAs

- **Questions :**

  debbie.cohen@pennmedicine.upenn.edu